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PHYSICAL ACTIVITY IN PARKINSON'S DISEASE – MEASUREMENT, CORRELATES AND EFFECTS OF BALANCE TRAINING

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Physical activity in Parkinson's disease – measurement, correlates and effects of balance training
THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Aim: The overall aim of this thesis was to investigate correlates of physical activity in older adults with Parkinson's disease and to evaluate the effects, both short- and long term, of the HiBalance program on physical activity and sedentary. Further, to investigate the associated factors of a training effect on physical activity. To this end disease-specific physical activity estimates are needed.

Methods: In **Paper 1** accelerometer cut points for different walking speeds were defined. Thirty older adults with mild-to-moderate Parkinson's disease walked at self-defined speeds of brisk, normal and slow speeds for three minutes in an indoor corridor. Walking speed was used as a reference measure, and cut points were generated using ROC curves. The cut points were cross-validated and Cohen´s quadratic weighted Kappa was calculated. In **Paper II**, correlates of both total physical activity and cut point-defined brisk walking were investigated by applying correlation analysis followed by multiple linear regression to accelerometer data. In **Paper III,** short- and long-term effects of the HiBalance program on physical activity and sedentary behavior were evaluated, using mixed analysis of variance and a multilevel model. Further, associated factors to a training effect on physical activity were investigated using a multiple linear regression.

Results: Optimal cut points for the vertical axis were ≤328 and ≥730 counts / 15 seconds for walking speeds at ≤1.0 m/s and >1.3 m/s, respectively. Sensitivity ranged between 68-100 %, with specificity between 75-82 %, whilst validation and Kappa analysis showed 74% absolute agreement and a substantial agreement of $\kappa = 0.79$ (95% CI 0.70–0.89), respectively. Exploration of correlates of total physical activity and amount of brisk walking led to two linear regression models. Motor impairment, physical function, body mass index and dyskinesia were significantly associated with total physical activity, explaining 34% of the variance, whilst physical function and balance control were significant factors related to brisk walking, explaining 22% of variance. Short- and long-term effect analysis revealed that brisk walking was the only factor showing a significant interaction effect of group and time. Moreover, the effect on brisk walking dissipated 6 months after intervention. Analysis of the training effect on physical activity revealed that intervention group affiliation and spring season were significantly associated to an increase in brisk walking, while increased balance after training was not.

Conclusion: This thesis provides cut points for physical activity measurement in older adults with Parkinson's disease. Results also suggest that correlates of total physical activity and brisk walking differ, and evidence of factors not previously shown to be associated with PA in this population, is provided. Moreover, the HiBalance program leads to an increased amount of brisk walking in daily living, yet this increase is not linked to improved balance control. Also, clinicians should be aware of the seasonal effect on ambulatory activity in this population, and that the intervention effect dissipates after half a year, thereby warranting recurrent training.

SAMMANFATTNING

Syfte: Det övergripande syftet med denna avhandling var att undersöka faktorer associerade till fysisk aktivitet hos äldre med Parkinsons sjukdom, samt att utvärdera kort- och långtidseffekter av HiBalance-programmet på mängd fysisk aktivitet och stillasittande. Likaså, att undersöka faktorer kopplade till en träningseffekt på fysisk aktivitet. För detta ändamål krävs sjukdomsspecifika estimat av fysisk aktivitet.

Metod: I det första delarbetet definierades tröskelvärden av accelerometerdata för olika gånghastigheter. Trettio äldre med mild till måttlig Parkinsons sjukdom promenerade i tre självdefinierade hastigheter av rask, normal och långsam gång, under tre minuter i en korridor inomhus. Som referensmått användes gånghastighet och tröskelvärden genererades med ROC-kurvor. Tröskelvärdena korsvaliderades samt evaluerades med hjälp av Cohens kvadratiskt viktade kappa. I det andra delarbetet undersöktes korrelat till total fysisk aktivitet samt tröskelvärdesdefinierad mängd rask gång, via korrelationsanalys följt av multipel linjär regression. I det tredje delarbetet användes variansanalys samt en flernivåmodell för att undersöka kort- och långtidseffekter av HiBalance-programmet på fysisk aktivitet och stillasittande. Likaså undersöktes associerade faktorer till en träningseffekt via en multipel linjär regression.

Resultat: Optimala tröskelvärden för den vertikala axeln var ≤328 och ≥730 counts per 15 sekunder för respektive ≤1.0 m/s och >1.3 m/s. Sensitiviteten definierades till 68-100% och specificiteten till 75-82% för respektive hastighet, medans validering och Kappa-resultaten visade 74% absolut överensstämmelse samt en betydande överenstämmelse på $\kappa = 0.79$ (95% CI 0.70–0.89) för tröskelvärdena. Undersökningen av faktorer relaterade till total fysisk aktivitet och mängden rask gång ledde till två linjära regressionsmodeller. Motorisk nedsättning, fysisk funktion, kroppsmasseindex samt dyskinesi var signifikant associerade och förklarade 34% av variansen av total fysisk aktivitet, medans fysisk funktion och balanskontroll sågs signifikant associera till rask gång, med en förklarad varians på 22%. Analysen av kort-och långtidseffekter visade att rask gång var den enda faktor som påvisade en signifikant interaktionseffekt mellan grupp och tid. Likaledes, effekten på rask gång upphörde sex månader efter träning. Analysen av träningseffekt på fysisk aktivitet visade att tillhörighet till träningsgruppen samt sommarhalvåret var signifikant associerat till en ökning av rask gång, dock ej en förbättrad balansförmåga.

Konklusion: Denna avhandling tillhandahåller accelerometertröskelvärden för mätning av fysisk aktivitet hos äldre med Parkinsons sjukdom. Övriga resultat visar att korrelat till total fysisk aktivitet och rask gång är åtskiljda, dessutom tillhandahålls ny evidens vad gäller korrelat till fysisk aktivitet hos denna grupp. Vidare redovisas att HiBalance-programmet ökar mängden daglig rask gång hos äldre med Parkinsons sjukdom, dock är denna ökning inte kopplad till ökad balansförmåga. Likaså bör kliniker vara medvetna om säsongseffekten på mängden rask gång och att effekten av träning upplöses efter ett halvår, vilket föranleder återkommande träning.

LIST OF SCIENTIFIC PAPERS

I. Nero H, Benka Wallén M, Franzén E, Ståhle A, Hagströmer M. Accelerometer cut points for physical activity assessment of older adults with Parkinson's disease. PLoS ONE. 2015, 10(9): e0135899.doi:10.1371/journal.pone.0135899.

II. Nero H, Benka Wallén M, Franzén E, Conradsson D, Ståhle A, Hagströmer M. Objectively assessed physical activity and its association with balance, physical function and dyskinesia in Parkinson's disease. J Parkinsons Dis. 2016 Oct 19;6(4):833-840.

III. Nero H, Benka Wallén M, Franzén E, Ståhle A, Hagströmer M. Effects of balance training on habitual physical activity and sedentary behaviour in older adults with Parkinson's disease.
In manuscript.

PAPERS RELATED TO THE THESIS

Conradsson D, Löfgren N, Ståhle A, Franzén E. Is highly challenging and progressive balance training feasible in older adults with Parkinson's disease? Arch Phys Med Rehabil. 2014 May;95(5):1000-3.

Benka Wallén M, **Nero H**, Franzén E, Hagströmer M. Comparison of two accelerometer filter settings in individuals with Parkinson's disease. Physiol Meas. 2014 Nov;35(11):2287-96.

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Conradsson D, Löfgren N, **Nero H**, Hagströmer M, Ståhle A, Lökk J, Franzén E. The effects of highly challenging balance training in elderly with Parkinson's disease: A randomized controlled trial. Neurorehabil Neural Repair. 2015 Oct;29(9):827-36.

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LIST OF ABBREVIATIONS

ADL	Activities of daily living
ANOVA	Analysis of variance
AUC	Area under the curve
BETA-PD	Balance, Elderly, Training, Activity in Parkinson's Disease
BMI	Body mass index
H&Y	Hoehn & Yahr
MET	Metabolic equivalent of task
MMSE	Mini-mental state examination
MVPA	Moderate-to-vigorous physical activity
PA	Physical activity
PAP	Physical activity on prescription
PD	Parkinson's disease
RCT	Randomized controlled trial
ROC	Receiver operating characteristic
SD	Standard deviation
TAC	Total activity counts
VM	Vector magnitude

1 FOREWORD

The importance of physical activity (PA) to people of all ages and backgrounds are nowadays regarded as more or less common knowledge. Due to its relevance to optimal health, it should be in all clinicians', trainers' and health professionals' interest to measure the extent of this behavior in their clients/patients. Many instruments have been developed, with more emerging, to capture this important behaviour. My idea of a great instrument is one that requires minimal amount of technical expertise from the end user, while being as exact as possible in its portrait of daily movement. As such, whilst working on this thesis I wanted to assist in the refinement of PA quantification using a commonly utilized accelerometer, for PA-measurement in older adults with Parkinson's disease (PD). Also, since PA is a behavior so strongly linked to health, and balance disturbances can be a major obstacle for people with PD to be active[1], I wanted to explore whether an intervention aimed at increasing balance performance could also yield secondary effects on PA. Hopefully the results presented here can aid clinicians in getting results of interest with maximum ease, as well as helping in the ongoing health care implementation of the intervention, in order for the person with PD to benefit.

2 INTRODUCTION

This thesis and the containing papers is part of a randomized controlled trial (RCT), conceptualised under the acronym BETA-PD (Balance, Elderly, Training and Activity in PD) project. Within this RCT, the primary aim was to test the HiBalance program on older adults with PD and specifically evaluate its effects on balance performance, gait velocity, fear of falling and PA (Step 2 in Figure 1).

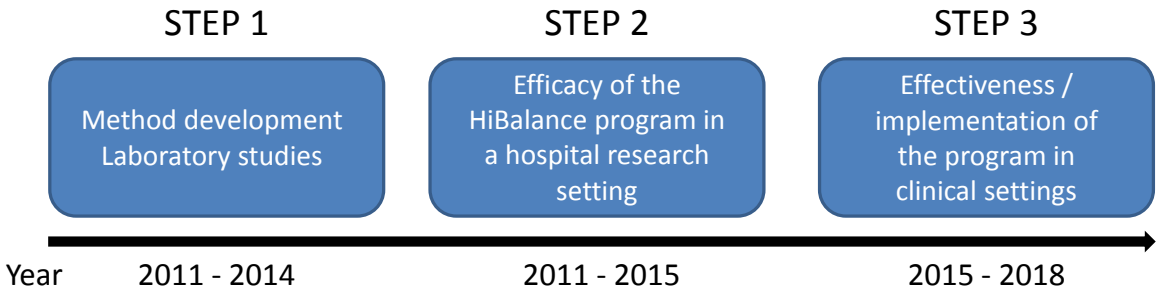

Figure 1. A graphical overview, including a time line, of the steps in the BETA-PD study.

2.1 PHYSICAL ACTIVITY

In a well-cited publication by Caspersen et al (1985), the terms PA, exercise and physical fitness were differentiated and defined, and PA was defined as *any bodily movement produced by skeletal muscles that result in energy expenditure*. Exercise on the other hand, was defined as a sub-category of PA that is planned, structured, repetitive, and has a final or

intermediate objective of improving or maintaining physical fitness. In this context, physical fitness is described as a set of characteristics that are either linked to health or skill, and relates to the ability to perform PA[2]. Different contexts or domains of the behavior are also of interest in the PA field of research, such as recreation, transportation, household chores, and/or occupation. As such, activity in any of these domains can be health-beneficial and is therefore officially recommended[3].

To study PA, one may use different dimensions to facilitate the description of the behavior. A common approach is the four part model, consisting of: mode that describes the type of activity performed; duration indicating the amount of time activity is performed; frequency of performed activity; and intensity of the activity[4]. Most recommendations or guidelines regarding PA for health improvement or disease prevention include a determined amount/level/type of each dimension.

The current thesis employed the above described definitions for each term, since they are not only commonly used, but may also be considered intuitive.

2.1.1 General effects of physical activity

The effects of PA on health (or more specifically the incidence of heart disease) has been known since the 1950's [5, 6]. Since then our knowledge continued to grow concerning the evidence of its highly potent ability to prevent and treat a large number of conditions and diseases[7]. Nowadays we know that chronic diseases such as cancer and cardiovascular disease, but also obesity, type 2 diabetes, stroke, depression and the risk of premature death are related to PA, or the lack thereof [3, 8]. Decades of research in areas of epidemiology (public health) and physiology has shown that PA has both economic, as well as health benefits, and that behavior change in different population groups is possible[9].

Since 1995 recommendations regarding the mode and amount of PA to engage in per day for achieving health benefits have been available[10], and has thereafter been updated[11]. The current recommendation is 150 minutes of moderate intensity PA per week (interchangeable with 75 minutes of vigorous activity) or 500 Metabolic Equivalent of Task (MET)-minutes per week (where one MET is equivalent of energy expenditure at rest) in a minimum of 10 minute bouts[7]. These recommendations established the dose-response relationship between PA and health, where those at the lowest level of activity enjoys the greatest health benefits, and that beneficial effects are additive with increased activity. According to a recently performed prospective cohort study, the minimum amount of moderate-to-vigorous PA (MVPA) per week necessary for a reduction in mortality, and an increased life expectancy, is 90 minutes, or 15 minutes per day (14% reduced risk of all cause-mortality and an extended life expectancy of 3 years)[12]. There is no recommendation for maximum threshold of activity, although benefits are believed to maximize at 3 to 5 times higher than recommended levels[13].

On the other side of the spectrum we find sedentary behavior, which in recent years has been up for debate in both scientific papers and media. This term is separate from the concept *inactivity*, where the latter was defined - in this thesis - as not reaching recommended levels of PA[14]. Since the 90's, sedentary behavior has been regarded as a major risk factor for coronary artery disease and cardiovascular mortality, and in recent years also been identified as a risk factor for a wide range of other health outcomes[15-18]. It has even been postulated that sedentary behavior involves some physiological mechanism, defining it as unhealthy regardless of whether it displaces other activities or not[19]. Sedentary, although a relatively subjective term, is commonly defined as any waking behavior characterised by very little body movement and an expenditure of energy <1.5 METs[20, 21]. The definition of the behavior thereby includes activities such as sleeping, lying down, sitting and most types of screen-based entertainment.

Although vastly researched, a lack of consensus continues to persist on whether sedentary has a unique detrimental effect on health. Studies suggesting a persistent relationship between cardio-metabolic deficits and sedentary have adjusted for PA and subsequently reported a unique effect of sedentary on health[15, 22]. However, Maher et al (2014) claims that previous studies often adjust for some sub-measure or specific intensity measure of PA and not the total activity spectrum[23]. This method is considered a limited way of analysis, and if total activity is used for adjustment, the original detrimental effect of sedentary dissipates, according to the researchers[23]. Whether sedentary behavior has a unique effect on health or not, it is still considered to be linked to incremental all-cause mortality. In response to the detrimental independent effect of sedentary, recent findings from a meta-analysis of pooled data suggest that high levels of moderate intensity activity (60-75 min per day) may eradicate the higher risk of death due to a large amount of sitting time[24]. Hence, if a large amount of sedentary per day is unavoidable, e.g. due to occupation requiring sitting, extra activity may help.

2.1.2 Correlates and determinants

Understanding the cause of PA behavior is essential when developing and designing public health interventions, as well as interventions for specific sub-populations. Since most aetiological PA-studies are cross-sectional in nature, statistical association, but not causation, is established[25] (Figure 2). Cross-sectional studies result in correlates, while determinants are established using longitudinal observational studies or experimental ones[25, 26]. To date there are several studies that explored correlates, as well as determinants, of PA in different populations and age groups, but mostly focusing on individual-level factors in high-income countries. Although correlates are specific for different domains (e.g. occupation, transportation, home-based activities etcetera)[27], the most common and clearest correlates found to be associated with PA in adults and older adults are health status and self-efficacy, with evidence corroborating their status as determinants as well[28-30]. Other correlates found to be relevant are age, sex, motivation and previous PA[26, 28, 29, 31].

In older adults, self-efficacy, PA-identity, social support, health condition, age and depressive symptoms have shown to be associated with PA[32-34], yet it seems that barriers and motivators may differ between active and inactive older adults[35]. An ecological model describing determinants of PA, incorporating intra- and interpersonal as well as environmental factors have been suggested, with each domain containing both modifiable and non-modifiable ones[26].

Although determinants may be of greater value for understanding the behavior and performing interventions, there are advantages to cross-sectional designs and the resultant correlates. They provide evidence of possible mediators for the planning of interventions, and may aid in analysing several variables with greater ease, providing evidence for improvement of intervention design[26].

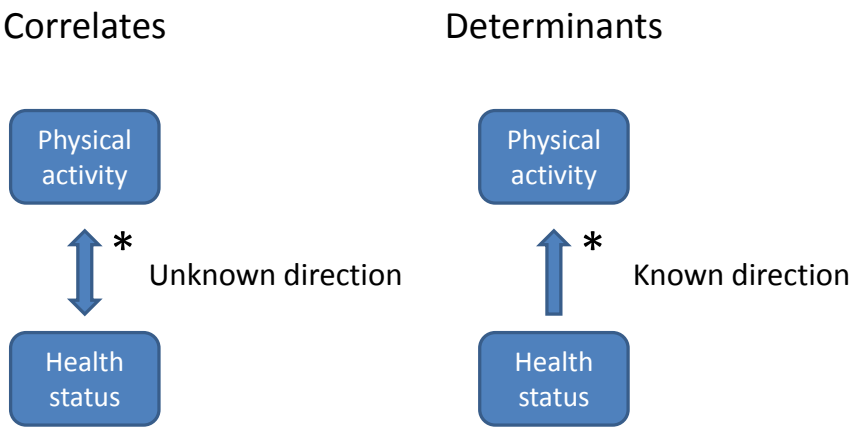

Figure 2. Schematic illustration of difference between correlates and determinants.

2.1.3 Methods of measurement

Behavior measurement can be challenging no matter what type of measure is chosen. Previously, the most common basic construct of interest when quantifying PA was energy expenditure, and with the development of new methods and measurements more quantitative and qualitative components have come into focus[36]. To document duration, frequency and intensity of PA necessary for evaluating the prevalence of people meeting PA recommendations, examining the effect of PA on specific health parameters, investigating dose-response and evaluating interventions, valid and reliable measurements are required[37]. When quantifying PA the choice of measure may be a compromise between accuracy and feasibility, and PA-questionnaires could in some contexts be the most feasible alternative, compared to interviews or wearable sensors[38] (Figure 3).

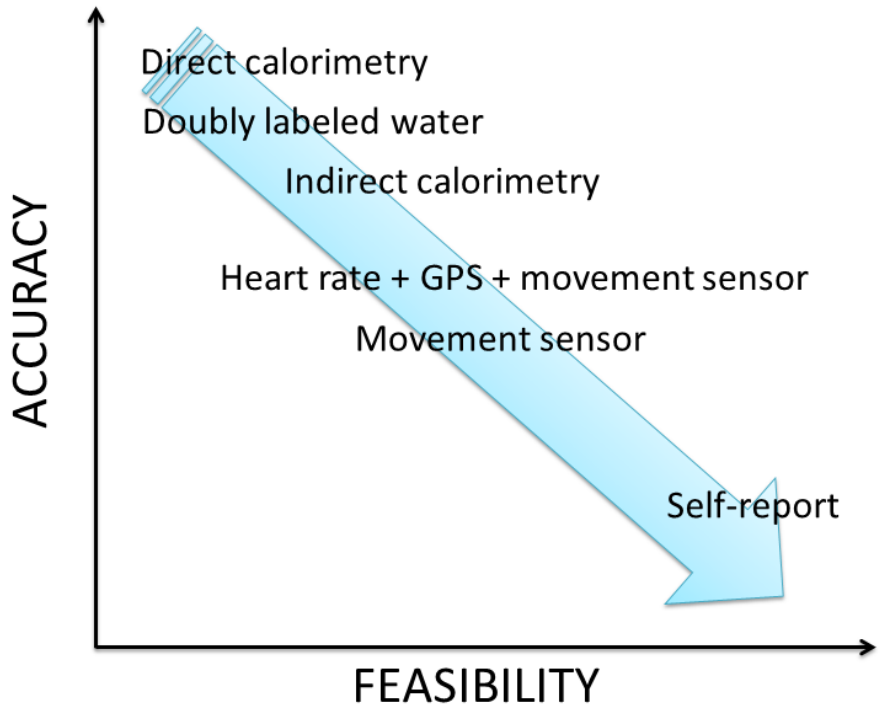

Figure 3. A schematic image of the trade-off between accuracy and feasibility in physical activity measurement.

Measures based on self-report (questionnaires, diaries, logs, recalls) are the most widely used when quantifying PA. They may include self- or interview-administered questionnaires or diaries and typically facilitates the collection of a vast amount of data from big populations[39]. With the use of self-report as a means of measuring PA comes some disadvantages. Social desirability may bias the result, just as cognitive impairment limiting the ability to recall, understanding of important terms, and ascertaining frequency, intensity and duration of activity may hinder the individual to provide an accurate description of his/her PA[39-41]. Adding on, in a systematic review on the reliability and criterion-related validity of PA-questionnaires (both existing and new), results showed that very few questionnaires boasted with both great reliability and validity, where the greatest flaw seemingly being validity, ranging from a coefficient of r = 0.25 to 0.41[37].

Objective PA measurement tools imply devices such as calorimetry, accelerometers, heart rate monitors and pedometers. These types of instruments have helped contribute to the understanding of PA as a health-related variable, and perhaps also reduced the human error incorporated in reporting and recall bias. Although the obvious advantages of the more objective measures, some of these are more costly and intrusive, and most also require expertise when utilized[42]. With time wearable monitors such as accelerometers and pedometers are becoming more common in PA research, since they provide a more exact measure of physiological or mechanical parameters corresponding to activity, in comparison to subjective methods[43]. Using a wearable sensor, such as an accelerometer with internal memory, enables for measurement of total amount, intensity, duration and frequency of PA, and for analysis of PA patterns over time[43].

Accelerometers record raw acceleration data in the unit of gravitation (g) in one or more axes (vertical, anteroposterior, lateral), or as a vector of the three axes (vector magnitude, VM) at a pre-set sample rate of several times per second (normally 30-100 Hz). The raw data is pre-filtered (through a band-pass filter to exclude non-human movement) and translated to a generic value or measure, sometimes referred to as counts. Counts are defined in a pre-selected epoch, and to interpret counts as a meaningful unit, data thresholds are used[36]. Thresholds, or accelerometer cut points are usually defined in validation or calibration studies. Most calibration studies have been performed in an environment that is controlled, and with protocols containing walking and/or running on treadmills, or based on structured activities. Collateral to this process, some physiological measure - thought of as a criterion measure (e.g. consumed oxygen) - is simultaneously collected[44]. Using statistical / mathematical methods, thresholds are then generated based on physiological intensity or specific activity. These cut-points, derived from laboratory studies, are often highly predictive when intensity is of interest, but have limited validity in a free-living setting[45]. Instead, it has been suggested that since accelerometers capture ambulation quite well, intensity could be translated to the biomechanical domain, such as referring a cut-point to a specific walking speed[44].

2.1.4 Intervention effects on physical activity

Although the convincing arguments around the benefits of increased PA are abundant, difficulties in translating evidence of correlates and determinants into an effective intervention continue to persist. To achieve programme maintenance and beneficial health effects, extensive knowledge on how to implement, adopt and sustain is essential[46]. Also, an understanding of available interventions is necessary.

Despite these problems, a meta-analysis has shown that there are effective interventions to increase PA, in fact, the included interventions showed an overall moderately large mean effect (Pearson correlation coefficient of 0.34). Also, the results reported that independently of sample size, the effects were moderated and larger when experimental design containing behavior modification was utilized, and the intervention was of short duration[47]. Adding on, papers based on previously performed RCT's containing either a training intervention or prescribed exercise have reported beneficial effects on physical fitness, PA and PA-energy expenditure in older adults[48-50]. The results suggest that fitness may be a key element, or at least a facilitating factor that increases habitual PA in this population. In a greater context, the results also propose factors to consider when choosing, designing or evaluating interventions.

A different example of intervention to consider is the use of pedometers as an instrument to encourage PA in daily living, which has increased in recent years. The instrument's popularity has steadily grown and recent accumulated findings show that using pedometers in an intervention is associated with increased PA (about 2000 steps per day) and that its use

is linked to health-enhancing advantages such as decreased blood pressure and weight reduction. However, the added factor of giving the pedometer user a defined step goal was essential, since the absence of it nullified any increase in PA[51]. This is in line with previously reported results, indicating that some form of attempt at behavior modification, prescription or activity goal is necessary for successful modification of PA.

2.1.5 PA in adults, older adults and individuals with a neurological disease

Depending on the choice of method for PA measurement, the conclusions of the activity level of adults in general may differ. In a Swedish cohort study consisting of 1114 adults measured using accelerometry, 52% accumulated 30 minutes of MVPA per day, but only 1% achieved this level via bouts of ≥10 minutes[52]. A recent review of PA levels in older adults reported a variation of the population reaching recommended levels, ranging between 2.4-82%. The variation was due to different definitions of recommended levels, as well as contrasting instruments. Although the level varied, in general older adults were less active than reference groups[53].

Many of the health benefits of PA for the general population also apply to people with certain health conditions or disorders. Since those afflicted can be at even greater risk of health risks associated with a sedentary life, the lack of PA is an even more acute problem in these population groups. According to estimations from the USA, levels of PA in individuals with disabilities (both physical and cognitive) are much lower, compared to those without disability, where an estimated 56%, compared to 36%, respectively, perform no leisure-time PA at all[7]. On the other hand, there is strong evidence suggesting that outcomes of mental health, cardiorespiratory- and musculoskeletal health typically increase by exercise in people with physical disabilities[7]. Hence the participation of PA may be hindered or at least aggravated due to disability, and the beneficial effects of PA may also be lacking, thereby increasing risk of more severe disease and further complications.

Stroke is one of the leading causes of adult motor dysfunction in the world and leads to the most hospitalizations when comparing neurological diseases[54]. As such, it is imperative to prevent and treat this disease with maximum efficiency. Findings suggest that an increased level of regular leisure-time PA serves as an important component of primary stroke prevention in both men and women[55, 56]. In post-stroke treatment, physical rehabilitation and exercise are first-line intervention strategies, since it may reduce chronic impairment by promoting neural organisation and reducing the volume of the infarct[57, 58].

More than 2.5 million individuals are afflicted by multiple sclerosis (MS), a demyelienating disease of the nervous system resulting in muscle weakness, fatigue, loss of balance, depression and declining cognitive function[59]. It is estimated that about 78% of people with MS are inactive, despite the recommendation of PA as a counter-agent to the disabling symptoms. These numbers are not due to a lack of interest in PA among the affected, but

rather a lack of knowledge among health-professionals regarding the appropriate and evidence-based amount of PA suitable[60]. The recommendations for people with MS have gone from advising no exercise to an evidence-supported stance advocating PA or exercise due to its beneficial effect on mobility, fatigue and quality of life[61]. Other reported beneficial effects of exercise include increased muscle strength, aerobic capacity, walking and balance[62].

Considering the evidence presented above and the fact that aging of individuals with disabilities of neurological character is a reality, it is important to acknowledge that with ageing comes the natural increase of sedentary, and it is of outmost importance to prevent inactivity as well as promoting PA and rehabilitating the affected through PA or some structured exercise intervention adapted to each individual.

2.2 PARKINSON'S DISEASE

In 1817, James Parkinson first described the patients with the clinical symptoms that would later be described with his name. About 100 years later, in 1919, it was discovered that patients with PD are deprived of cells in the substantia nigra, and in 1957, the neurotransmitter dopamine was discovered by Dr. Carlsson in the beautiful city of Lund, southern Sweden[63]. Since then, the knowledge surrounding the disease and its etiology has grown steadily. There are several neurological conditions sharing some clinical manifestations, with the focus of idiopathic PD being described and studied in this thesis.

2.2.1 Symptoms, incidence and prevalence

Idiopathic PD is of a neurodegenerative nature and its pathophysiology is defined by early death of dopaminergic neurons in the substantia nigra pars compacta. As a result, the deficiency of dopamine leads to the manifestation of what is called parkinsonian symptoms[64]. The clinical manifestations of PD are often described by the four cardinal symptoms, with the acronym TRAP: Tremor at rest; Rigidity; Akinesia; and Postural instability. However, there are several other common symptoms or manifestations related to the disease, both motor and non-motor, including, but not limited, to the following: freezing of gait; flexed posture; depression; cognitive decline/dementia; autonomic dysfunction; anxiety; and sleep fragmentation/insomnia[65]. The diagnosis of PD is normally based on observed symptoms resembling the cardinal symptoms (TRAP) and/or other visible motor manifestation such as shuffling gait, combined with response to Levodopa[66].

The prevalence of PD is one of the highest among the neurodegenerative diseases and increases with age, starting at (all per 100 000) 428 for 60 to 69 year olds and continuing up to 1087 for 70 to 79 year olds[67]. The incidence also rises with age and has been reported as 13.4 per 100 000 person-years if age- and gender adjusted, with a peak in incidence

between the ages of 70-79 years[68, 69]. Males have a higher incidence in all age groups. Furthermore, it has been postulated that the amount of diagnosed people will increase continually in Europe over the next 15 years[70].

2.2.2 Disease progression

Non-motor symptoms are normally present before onset of the more typical motor manifestations, such as rapid eye movement sleep behavior disorder which occurs on average 12-14 years before motor symptoms[71]. Later the progression of disease is portrayed by worsening of symptoms related to motor function, usually treated using symptomatic therapy[64]. Disease severity is clinically classified using the Hoehn & Yahr (H&Y) disease scale, where a high level of impairment is coupled with a heightened experience of activity limitations[72]. The scale ranges from one to five, where higher class signifies greater impairment (Table 1). With time, long-term side-effects of treatment appear such as motor fluctuations, dyskinesia and psychosis[73], as well as axial motor symptoms such as freezing of gait, balance dysfunction/postural instability, falls and dysphagia[64].

Table 1. The Hoehn & Yahr scale.

1	Unilateral involvement only usually with minimal or no functional disability
2	Bilateral or midline involvement without impairment of balance
3	Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent
4	Severely disabling disease; still able to walk or stand unassisted
5	Confinement to bed or wheelchair unless aided

2.2.3 Balance impairments in PD

Being active in daily living is important to maintain health, and in people with PD, gait and balance impairments that develop over time may hinder activity, thereby having a large effect on health related quality of life[74, 75]. Posture and balance are pillars of the ability to walk and stand, and balance (or postural) control has been defined as maintenance of equilibrium of the body in relation to the force of gravity under both dynamic and static conditions[76]. A perhaps more advanced interpretation of balance control comes from Horak et al (2006), where balance/postural control is defined as a complex skill based on different sensorimotor processes interacting dynamically, where the goals of postural behavior include orientation and equilibrium of posture[77]. Balance impairment can be present early

in PD, and its association to falls and fear of falling potentially adds to the effect of undermining activity and independence[78]. Roughly, one third of individuals with PD develop balance impairment during the first two years after diagnosis[76], and the manifestations of balance problems in PD is believed to be evident in four domains, namely balance during quiet stance, reactive postural adjustments, anticipatory postural adjustments and dynamic balance[79]. Evidently, balance impairment responds poorly to medical or surgical treatment, such as Levodopa and deep brain stimulation[80]. Thus, other treatment and rehabilitation options for older adults with PD are of major importance.

2.2.4 Balance training

There is evidence of the benefits of physical therapy for balance performance, showing minimal clinical important changes[81]. Exercise therapy focusing mainly on components of balance impairment, i.e. balance training, show moderate to high effect sizes[79]. As a matter of fact, intervention programs incorporating highly challenging balance exercises demonstrate to a greater extent an improved performance of activities related to balance, compared to other types of programs. Yet, there is no effect on proportion of fallers[82]. It has been proposed that long term follow-ups of balance training interventions are performed to determine the trajectory of change over time, and perhaps also cost-effectiveness, preferably using some randomized controlled trial of greater quality and size[81, 83].

2.2.5 Hypothetical effects of balance training on physical activity

The reports of beneficial effects of PA or exercise on balance control in older adults are numerable[84-88], yet there are fewer investigating the inverse relationship. Currently available findings report a short term effect of balance training on habitual PA in older adults with osteoporosis and in older adults with PD, where outcomes in both studies were based on steps/day[89, 90]. Suggestions have been made that retaining balance control may allow people with PD to stay active in daily living. Since there is evidence of training/exercise effects on gait and gait-related activities in PD[82, 90, 91], together with results showing beneficial effects on depression and cognitive decline[3, 8], this may also have beneficial fallout on level of habitual PA in older adults with PD. Studies have shown an association between greater exercise ability and higher level of habitual PA and greater balance control[92]. Adding on, frequent fallers tend to have a greater amount of limitations in activities of daily living (ADL) leading to a lower ability to perform common day-to-day activities, and also a greater fear of falling, shown to be associated with lower levels of habitual PA[93]. Therefore, by performing balance exercises it may be possible to increase or at the very least retain ones level of daily activity, despite functional limitations. Investigations are needed to confirm or reject these assertions, since the relationship between balance control and PA may be influenced by mediating factors.

2.3 PHYSICAL ACTIVITY IN PD

Previous research has shown that in general, individuals with PD do not reach the recommended amount of PA [94-96]. The desirable effects of PA are also available for people with PD, as reviews of the literature have concluded beneficial effects on mobility, gait, balance and muscle strength[97-99]. When considering more structured PA, people with PD who exercise have higher self-rated mobility and self-efficacy, and are less depressed in comparison to those not exercising[100]. Exercise may also improve the dopaminergic system and optimize drug efficiency[94]. Adding to the discourse, both experimental and basic research has shown that high-intensity exercise may promote neuroplasticity in areas of the brain affected by PD[101-104]. Furthermore, the non-motor symptoms related to PD, such as depression, sleep disturbance and cognitive decline, may all add to the risk of adopting a sedentary lifestyle, which may start a vicious circle, considering that inactivity may negatively affect clinical manifestations of the disease[94]. Hence, sedentary may accumulate and increase the risk of comorbidities and mortality (Figure 4).

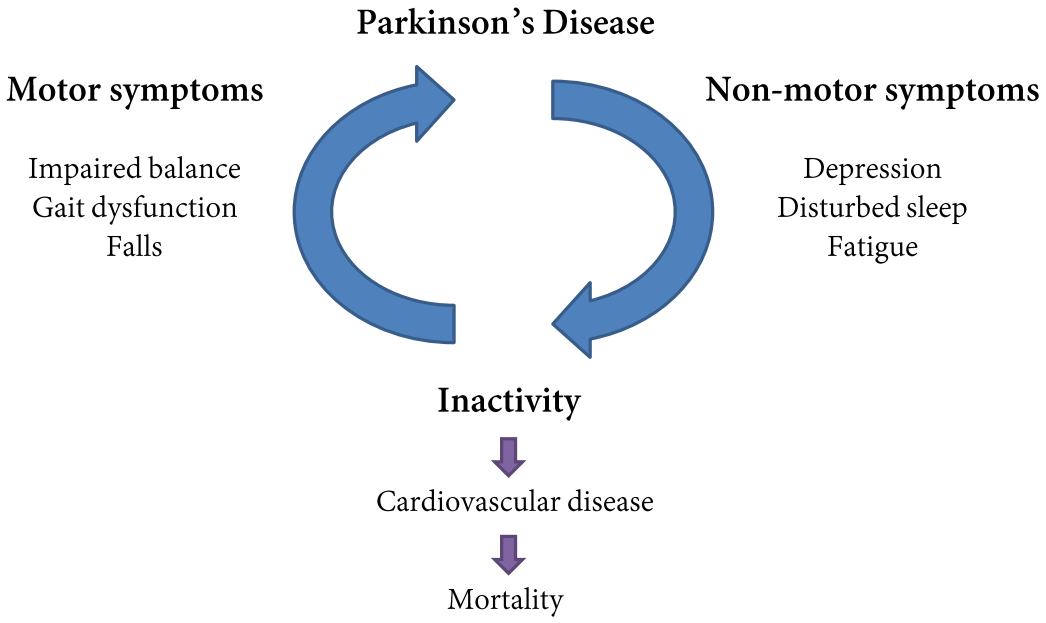

Figure 4. Symptoms of PD and the vicious circle. Inspired by Speelman et al (2011)[94].

Most studies investigating activity have used subjective measures, probably due to the ease of administration, lower costs or sample sizes that have been of a magnitude that hinders objective measurement. However, the tide is turning and objective measurement is becoming more common. In a systematic review performed by the author in 2015 (unpublished) with the aim of gathering articles reporting objectively measured habitual PA in older adults with PD, 13 studies were found in the literature. After initial quality control and exclusion of those not reaching general recommendations of what constitutes valid number of measured days / measurement period and hours / day, as well as those publishing more than once on the same cohort, seven papers remained (Table 2).

Table 2. Studies of objectively measured habitual weekly physical activity in older adults with Parkinson's Disease, available in the Pubmed, Cochrane and Web of Science databases in 2015.

Paper	Quality[a]	Type of measure	PD population[b]	Total PA[c]	Health-enhancing PA[d]	Reached recommendations (%)[e]
Benka Wallén et al, 2015[105]	High	Accelerometer, Actigraph	PD, mild to moderate	293 614 TAC	16.4 min/day	27%
Dontje et al, 2013[106]	Average	Accelerometer, TracmorD	PD, mild to moderate	510 mean kcal/day	17.8 min/day	15%
Ford et al, 2010[107]	Average	Pedometer, StepWatch3	PD, mild to moderate	8996 steps/day	-	*Inconclusive*
Hale et al, 2008[108]	Average	Accelerometer, RT3	PD, minimum 6 months since diagnosis	122 094 MVM[f]	-	*Inconclusive*
Lord et al, 2013[109]	Average	Accelerometer, ActivPAL	PD, mild to moderate	5452 steps/day	5,1 min/day	21%
Rochester et al, 2012[110]	High	Accelerometer, ActivPAL	PD, advanced	2259 steps/day	-	*Inconclusive*
van Nimwegen et al, 2013[111]	High	Accelerometer, Tracmor(D)	PD, mild to moderate	458 kcal/day	-	*Inconclusive*

[a]Defined using a checklist based on Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) observational study checklist[112] and Tooth et al[113]. [b]Description of the population from which the sample was drawn. [c]Total activity counts (TAC) or steps per day. [d]Mean amount per day. [e]10 000 steps / day or 30 min of moderate to vigorous PA / day. [f]Mean vector magnitude.

Of these seven, only three reported some measure of MVPA or number of participants reaching recommendations. The low number of studies suggests further investigation of level of PA in this group. Although no greater conclusion should be drawn from these few papers, the results display a population not reaching recommended levels of PA, and in dire need of effective interventions.

2.4 RATIONALE FOR THIS THESIS

Due to the importance of PA for older adults with PD, a need for valid, reliable and clinically accessible ways of measuring PA objectively is apparent. Accelerometry is a method increasing in popularity, with the Actigraph accelerometer being one of the most utilized instruments. Using cut-points to define different levels of activity is a common methodology in objective measurement, due to it being an accessible and easy way to quantify and analyse free-living PA[114]. Individuals with PD usually develop gait disorders, such as increased inter-stride variability, reduced walking speed with increased cadence, decreased step length, and gait hypokinesia that worsens as the disease progresses [115, 116]. When measuring PA objectively, such as with an accelerometer, an altered gait presumably influences the measurement and induces a measurement error if cut points generated from healthy adults are used during analysis. This potential error might affect the defined levels of time in different activity levels when measurements on individuals with PD are analysed, hence modifying conclusions based on the data. Since specific cut-points for PD have been lacking, the need for a calibration is essential, in this case of one of the most commonly used accelerometers.

To properly understand a behavior such as PA and design interventions influencing it, it is essential to fathom what influences the behavior and find modifiable factors that are associated. Associated factors of PA have previously been explored in PD, but the variance of PA has only been partly explained, highlighting the need for further exploration of correlates[95]. Adding on, since there is a proposed association with balance control and habitual PA and ADL, the effects of a highly-challenging balance training program on PA in older adults with PD is of great clinical interest. Mild-to-moderate disease severity is of specific interest, since although balance and mobility impairments are apparent, ambulation is still independent. If successful in increasing health-enhancing PA through this program, it may supplement the arguments for implementation into clinical practice. Also, if long term effects are investigated, indications as to how often older adults with PD need to train to keep potential effects may become apparent.

3 AIMS

The overall aim of this thesis was to investigate correlates of PA in older adults with PD and to evaluate both short and long term effects of the HiBalance program on PA and sedentary behavior. A further aim was to investigate the associated factors to a training effect on PA. To this end disease-specific physical activity estimates are needed.

3.1 SPECIFIC AIMS

Paper I: The objective of the study was to define and validate accelerometer cut points for both the vertical axis and vector magnitude (VM) for different walking speeds in older adults with mild-to-moderate PD.

Paper II: The aim was to investigate demographic, disease- and mobility-related factors that associate with objectively measured PA in a sample of older adults with mild-to-moderate PD.

Paper III: This paper aimed to investigate short-and long term effects of the HiBalance program on total PA, amount and bouts of brisk walking, and sedentary behavior. A further aim was to examine factors associated with a training effect on PA.

4 METHODS

4.1 STUDY DESIGN

Paper I is a methodological calibration study of the accelerometer of choice, with **Paper II** founded on a cross-sectional study and **Paper III** describing a randomized controlled trial with short- and long-term follow up, evaluating the HiBalance program (the BETA-PD study; clinical trial number NCT01417598).

4.2 ETHICAL APPROVAL

Ethical approval for all studies contained within this thesis was obtained from the Regional Board of Ethics in Stockholm (DNR 2006/151-31, 2009/819-32, 2010/1472-32, 2011/37-32 and 2012/1829-32). These studies were conducted according to the Helsinki Declaration (ethical principles for medical research involving human subjects), and all participants provided written informed consent before their inclusion. Furthermore, to compensate participants in the control group of the RCT for not receiving the intervention during the trial, they were offered to take part in the training program after the completion of the study.

4.3 PARTICIPANTS

4.3.1 Recruitment

In **Paper I**, participants for the study were recruited using advertisements at the local hospital and via patient organisations. The measurements were performed during autumn of 2013. For **Paper II** and **Paper III**, recruitment was performed using advertisements in local newspapers and notices at private neurological clinics and local hospitals. A majority of the participants (70%) were recruited using advertisements. Data were collected during spring 2012 to summer 2014.

Inclusion criteria for the study in **Paper I** were: ≥60 years of age; a clinical diagnosis of idiopathic PD (Queens Square Brain Bank criteria)[117]; and mild-to-moderate disease severity (H&Y-score 2-3)[118]. Participants were excluded if a need for any walking assistance or aids was apparent or reported or if they were unable to perform nine minutes of independently executed walking indoors.

Eligible participants for the BETA-PD study (**Paper II** and **III**) were women and men ≥ 60 years of age with a clinical diagnosis of PD according to Queens Square Brain Bank criteria[117] and a H&Y-score of 2-3[118]. Other criteria were having the ability to ambulate indoors without walking aid, impaired balance according to a clinical assessment performed at baseline and ≥3 weeks of stable dopaminergic medication. Exclusion criteria were: a

Mini-mental state examination (MMSE) score <24[119] signifying a cognitive deficit, and other medical conditions that would considerably influence balance performance or participation in the intervention. Background characteristics of all participants are presented in Table 3.

Table 3. Participant characteristics of all included papers in this thesis.

	Paper I	**Paper II**	**Paper III[1]**	
			Training	**Control**
Descriptive variables	**n=30**	**n=91**	**n=43**	**n=40**
Age, years	73 (5)	73 (6)	72 (6)	74 (6)
Sex – female (%)	13 (43)	39 (43)	16 (37)	20 (50)
BMI, kg/m²[a]	24.6 (3)	26 (4)	25 (4)	25 (5)
PD duration, years	6 (3-9)	5 (2-8)	5 (2-10)	5 (2-8)
H & Y score (%)				
- 2	15 (50)	39 (43)	20 (47)	15 (38)
- 3	15 (50)	52 (57)	23 (53)	25 (62)
LED[b]	693 (374)	573 (238)	584 (290)	649 (420)
Balance control[c]	-	19 (3)	19 (3)	18 (3)
UPDRS motor[d]	36 (8)	37 (11)	37 (11)	37 (11)
UPDRS ADL[e]	16 (5)	14 (5)	15 (4)	13 (5)

Characteristics presented as means (SD), median (25th-75th percentile) or frequency (%). [1]Data from baseline assessment. [a]Body mass index. [b]Levodopa equivalency dose, mg/day according to Tomlinson et al (2010)[120]. [c]Mini-BESTest total score. [d]Unified Parkinson's Disease Rating Scale - part III. [e]Unified Parkinson's Disease Rating Scale – Activities of Daily Living.

4.3.2 Sample size estimation

Sample size for the study described in **Paper I** was based on previous calibration studies influenced by its methodological nature and lack of effect from which to base power calculation upon. Also, the utilization of a leave-one-out cross-validation enabled all participants to remain while still validating the results. Previous comparable studies have included between 18 and 38 participants[121-124]. For **Paper II** and **III,** sample size estimation was based on a pilot study of the HiBalance program[125] as well as similar studies performed in this population[126, 127]. To calculate power (80% at a 2-sided alpha level of 5%) three outcome measures were used: the Falls Efficacy Scale (FES-I), Mini-BESTest, and gait velocity. The final number of 100 participants in the RCT was determined by estimating a 15% drop out and correcting for long term follow-up.

4.3.3 Paper I sample

For this methodological study, a total of 31 older adults with PD were assessed for inclusion. During testing, one individual was excluded due to sudden illness, hence the sample finally contained 30 individuals (13 women). Moreover, one participant did not partake in all walking bouts due to fatigue, which led to missing data for this individual.

4.3.4 Paper II and III sample

For the RCT of the BETA-PD study, a total of 100 included participants were divided into two geographic cohorts, based on home address (either north or south due to hospital localisation). After initial baseline procedures/testing, the participant was randomized to either the intervention- or control group, using sealed opaque envelopes, entailing that both tester and participant were blinded. Since the persons acting as testers also served as trainers during the intervention, blinding of testers at the time points after baseline was not possible. However, trainers never acted as testers for individuals who had been part of the intervention group that they led in exercise. Of the 100 included and randomized participants, 76 completed the final 12 month follow-up (Figure 5). While this number completed the whole study, only 66 participants contributed with PA-data at 12 months, due to invalid or missing accelerometer data.

In **Paper II**, three participants with baseline accelerometer data from the pilot study were added, resulting in a total of 91 participants. Furthermore, in **Paper III,** participants who were excluded from the HiBalance program (n=5) was removed from analysis, hence baseline numbers differ between **Paper II** and **III**.

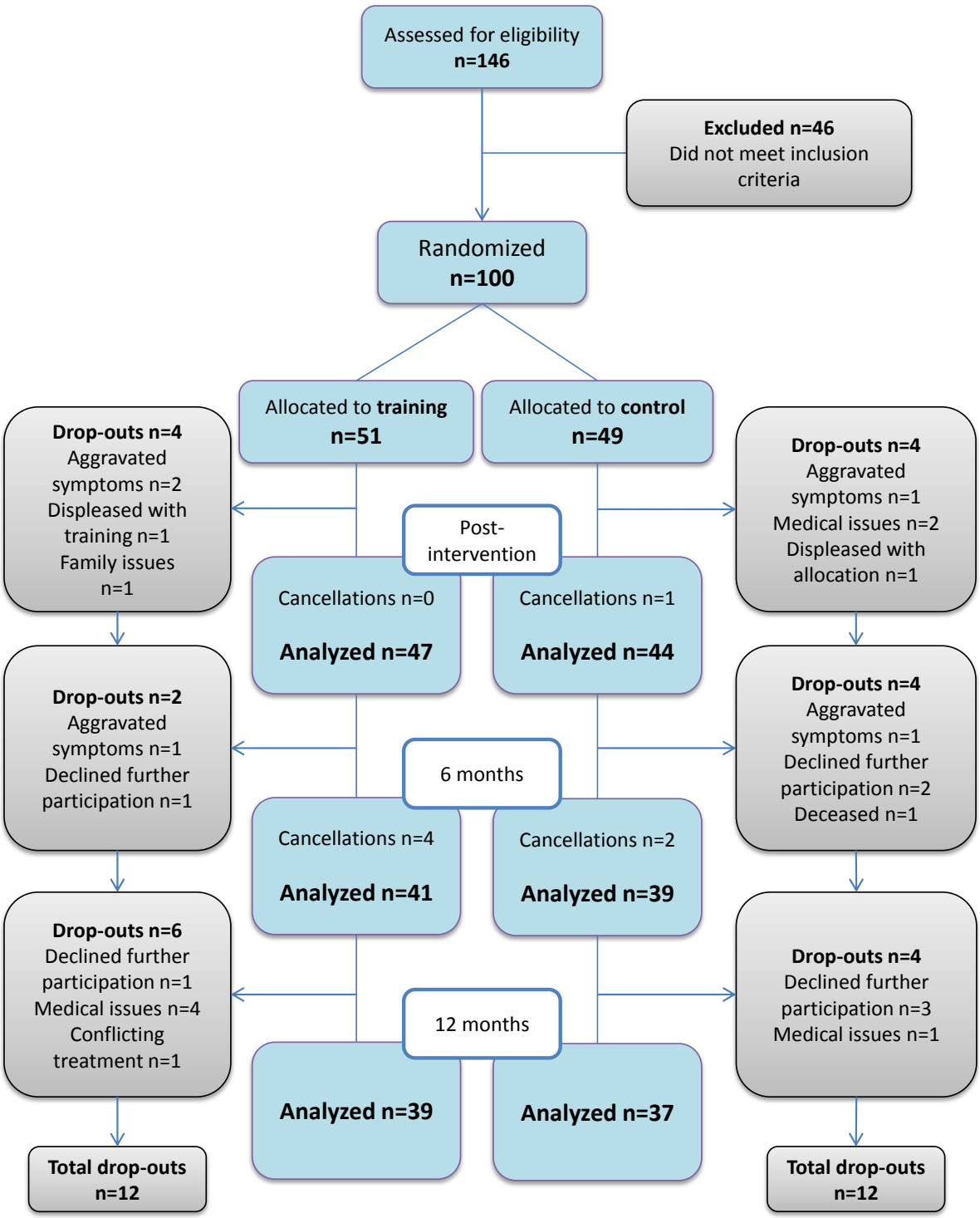

Figure 5. Flow chart of participants in the RCT of the BETA-PD project.

4.4 DATA COLLECTION

A wide variety of assessment tools and measurements were used to gather data for the three papers, with analysis focusing on describing the samples as well as measure effects of the intervention. A summary of all outcomes and measurements used in the studies can be seen in Table 4.

Table 4. Assessments included in the papers of the thesis.

Assessments	Paper I	Paper II	Paper III
Accelerometers	•	•	•
UPDRS motor[1]	•	•	•
UPDRS ADL[2]	•		•
Electronic walkway[3]		•	•
Mini-BESTest		•	•
FES-I[4]		•	
GDS[5]		•	
SF-36[6]		•	
PDQ-39[7]		•	
FOGQ[8]	•		
LED[9]	•	•	•
BMI[10]	•	•	•
Self-reported falls		•	

[1]United Parkinson's Disease Rating Scale motor score (part III). [2]United Parkinson's Disease Rating Scale – Activities of Daily Living. [3]GaitRITE mat. [4]Falls Efficacy Scale – International. [5]Geriatric Depression Scale. [6]Swedish Short Form-36 Health Survey. [7]Parkinson's Disease Questionnaire. [8]Freezing of Gait Questionnaire. [9]Levodopa Equivalency Dose (mg/day). [10]Body Mass Index (kg/m^2).

4.4.1 Physical activity measurement

Throughout all three studies, PA was measured using the Actigraph GT3X+ (Actigraph, Pensacola, FL). The GT3X+ is a small, lightweight accelerometer that registers acceleration in a raw format with a dynamic range of +/- 6 G and at a sample rate of 30 – 100 Hz. The raw data are defined in the unit of gravity and passes through a band-pass filter to eliminate non-human artefacts, or noise. At the moment, the user can choose between two filter algorithms, the standard filter or the Low Frequency Extension (LFE) option. The LFE increases the sensitivity to very low amplitudes, thereby theoretically increasing the possibility to sample movement from populations with slow movement or light steps. After data collection, all post-processing of data (filter choice, epoch length etcetera) was performed in the appurtenant ActiLife (Actigraph, Pensacola, FL) software.

In the studies within this thesis, the accelerometer was worn around the waist, attached to an elastic belt. For the weekly measurements in **Paper II** and **III**, it was worn by the participants for all waking hours and only removed when going to bed or during showers or baths. A log sheet where participants noted the time when the accelerometer was applied and removed was used for every measurement, and handed to the study coordinator after performed measure. It was also asked of the participant to note day and time of any activity or sedentary behavior that was not standard every-day occurrences, such as being sedentary a whole day due to traveling. At every measurement occasion participants were instructed on how to attach, wear and remove the accelerometer and the elastic belt. A brief instruction manual was also given to the participant which they could take home.

Accelerometer data were downloaded using ActiLife and processed with the standard filter settings, all according to published recommendations[128]. For **Paper II** and **III**, an epoch of 15 seconds was used, and non-wear time was defined as ≥90 minutes of consecutive zeroes which was subsequently removed from analysis. Spike tolerance (the allowance of small intervals of non-zero counts within non-wear time) and small-window length (up- or downstream window of consecutive zero-counts) was set to 2 minutes and 30 minutes, respectively[129]. After post-processing in ActiLife was completed, the data were transferred to a Microsoft Excel (Microsoft, Washington, US) spreadsheet to enable visual comparison of collected data with log sheet. By comparing data with logged time, all data collected during non-wear could be removed (e.g during accelerometer transport after wear period). Days containing <540 minutes of wear time was flagged and then excluded, and as thresholds for a valid measurement period, a minimum of four and maximum of seven days was used[105, 130-132]. Participant data with <4 days were excluded, as well as any days exceeding the seventh.

The result of **Paper I** led to quantification of the brisk walking speed threshold, which was utilized to calculate outcome variables in **Paper II** and **III**. The threshold for ≤1.04 m/s was used as a lower cut-off for calculating minutes of brisk walking. The primary outcomes in **Paper II** was total PA, defined as total activity counts per day of the vector magnitude (TAC), and activity corresponding to minutes of brisk walking per day. The latter was defined using the threshold of >328 vertical axis (Y-axis) counts/15 second epoch. For **Paper III**, outcome variables were total PA represented by TAC, minutes of brisk walking, bouts of brisk walking, sedentary time and sedentary bouts. Sedentary time was derived using cut-point thresholds for older adults from Aguilar-Farías et al (2014)[133], and bouts of sedentary and brisk walking was defined as any continuous bout lasting within the specific threshold for ≥10 minutes[134].

4.4.2 The Unified Parkinson's Disease Rating scale

The motor part of the Unified Parkinson's Disease Rating Scale (UPDRS-motor)[135], which assess common symptoms observed in PD such as rigidity, tremor, bradykinesia, gait and

postural stability, was used as an indicator of disease severity. It contains 27 items which are summarized as a total score (of 108 points), where a higher score indicates a greater degree of severity. It has been thoroughly tested for different types of validity and reliability, yielding satisfactory results[136]. Within the UPDRS-motor is the retropulsion test, which is used to assign a Hoehn & Yahr-classification corresponding to the disease severity of the patient. Although heavily weighted towards postural instability and therefore not encompassing a greater image of symptoms, it is widely used and fulfils some reliability and validity criteria[72].

Activities of daily living (ADL) were assessed using the UPDRS-ADL (part II), measuring disease related ADL, or motor disability[136]. It is a questionnaire comprising 13 items and may be used either in interview form or by self-report. The items cover questions regarding the self-perception of bodily functions, such as speech and swallowing, as well as activities like walking and making the bed. In the studies of this thesis, an interviewer recorded the self-assessed score on the ordinal scale ranging 0-4.The sub-scores were then summarised to a total, where a higher score equals more severe problems. The scale has been proven both valid and reliable for individuals with PD[137].

4.4.3 Balance control

To measure balance control the Mini-BESTest was used, a clinical test encompassing 14 items and covering four theoretical components of balance; postural responses, stability in gait, anticipatory postural adjustments and sensory orientation[138]. Sub-scores are based on a three-level ordinal scale from 0 to 2 (0 = unable or requires help, 2= normal), with a maximum score of 28. The validity and reliability of the Mini-BESTest have been tested and proven to be of acceptable standard for older adults with PD[139, 140].

4.4.4 Gait

The measurement of gait was performed using the electronic walkway GAITRite (CIR Systems, Inc., Haverton, PA, USA). The nine meter walkway is equipped with pressure sensors and connected to a computer, hence enabling collection and analysis of temporal as well as spatial gait parameters, such as gait speed and step and stride length. The GAITRite has been determined valid and reliable for the measurement of gait performance in individuals with PD[141, 142].

4.4.5 Physical function

For the self-assessed measure of physical function, the sub-score Physical Function (PF) from The Swedish Short Form-36 Health Survey (SF-36), as well as the sub-domain

Mobility from the Parkinson's Disease Questionnaire (PDQ-39) were used. Both SF-36 and PDQ-39 are self-administered questionnaires and cover eight dimensions of health and function. The more PD-specific questionnaire, PDQ-39, envelops areas reported by individuals with PD as adversely affected by the disease. An important difference between PDQ-39 and SF-36 is the score interpretation, where a lower score of the PDQ-39 indicates better perceived health, and vice versa for the SF-36. Furthermore, the two scores each contain 10 items related to the own perceived ability to be mobile and active in daily life. The SF-36 has been proven valid and reliable across many medical conditions[143-145]. The PDQ-39 is the most used and thoroughly tested scale of health-related quality of life in PD, and has been tested in countless cultural settings. It has satisfactory validity and reliability and is the current recommended measure for individuals with PD[146].

4.4.6 Dyskinesia

During the UPDRS-motor testing, potential dyskinesia in any part of the body was assessed, graded on a five grade scale (5=severe, 0= none), and noted. In **Paper II**, dyskinesia was dichotomized (1= dyskinesia in any part of the body, 0= no dyskinesia) due to uneven distribution.

4.4.7 Falling

During the interview process of the BETA-PD study, the number of falls was retrospectively reported by the participant. The fall data variable was dichotomized, where ≥2 falls during the last 12 months classified the participant as a recurrent faller[147]. The definition of a fall was an unexpected event in which the participant came to rest on the ground, floor or a lower level[148].

4.4.8 Depression

The Swedish version of the Geriatric Depression scale (GDS) was used as an assessment of depressive symptoms[149]. The Swedish GDS includes 20 questions with dichotomous response options and has previously been used for assessment of older adults with PD[150]. The measure has been deemed a valid and reliable self-rating depression screening scale for older adults[151, 152].

4.4.9 Concerns about falling

Concerns about falling were assessed using the Falls Efficacy Scale - International (FES-I), a self-administered questionnaire covering the performance of 16 specific in-and outdoor

daily activities[153]. Each item is scored on a scale of one to four of which a total score (16-64 points) is calculated, with a higher value indicating greater concerns about falling. The scale has been shown to hold satisfactory psychometric properties[154].

4.4.10 Freezing of gait

Freezing of gait was assessed using the Swedish version of the Freezing of Gait Questionnaire (FOGQ). The FOGQ is administered by the clinician, where the individual with PD self-rates the level of FOG experienced in daily living. The scale contains six items with five scale steps, which is summed to a total score (higher score equals greater symptoms). The validity and reliability of the scale have been tested, indicating adequate measurement properties[155].

4.5 PROCEDURES

4.5.1 Paper I

The assessment and data sampling took place at Karolinska Institutet in Huddinge, Sweden and were led by a physiotherapist that was well familiar with the methods. A pre-designed protocol was followed where participants were first informed of the study and how data would be managed and stored, after which written informed consent was obtained. Weight and height were measured using an electronic scale and a stadiometer, followed by an interview that was conducted where all questionnaires were completed. Next, tests related to disease severity were performed, followed by the participant being fitted with a heart rate monitor belt around the chest (underneath clothing) and an accelerometer - attached to an elastic belt around the waist. Participants wore regular in-door clothing and shoes. A walking trial was performed, where the participants briefly practiced walking at their self-defined speeds of brisk, normal and slow speeds, as well as estimating their perceived exertion on the Borg's Rating of Perceived Exertion (RPE) scale. Thereafter the test session was initiated, where participants walked in an in-door circular hallway for three minutes, at the three self-defined speeds. Between each walk the participant rested until the heart rate reached pre-walking levels. Before and after each walk, the participant rated the exertion using the RPE scale, and the physiotherapist documented the present heart rate.

4.5.2 Paper II and Paper III

Baseline measures of the included participants were performed in a movement analysis laboratory at Karolinska Institutet, Huddinge, Sweden. The testing comprised two parts, interviewing and administration of questionnaires, and measurement performed in the laboratory. After testing, each participant was allocated to either the intervention or control

group, using sealed and numbered opaque envelopes to ensure blinding. Prior to randomization which was performed in blocks of four, the participants were required to choose geographical cohort (north or south, based on living location). Each cohort had separate randomization envelopes. If randomized to enter the intervention group, the participant entered the HiBalance program, entailing 10 weeks of highly progressive and challenging balance training. At the end of the program (three months later), all participants were called for testing. The same procedure of testing was repeated six and 12 months after intervention.

4.6 INTERVENTION

The intervention of the BETA PD study, the HiBalance program, was conducted in groups of 4-7 participants. The 10-week program was performed for an hour, three times per week, and a minimum of two physiotherapists supervised the training. The program entailed four theoretical components of balance and gait: Sensory integration (tasks of walking on varying surfaces with or without visual constraint); Anticipatory postural adjustments (voluntary arm/leg/trunk movements focusing on movement velocity and amplitude as well as transitions of posture); Motor agility (coordination of the whole body during variation of gait conditions and reciprocal movements and quick shifts of movement characteristics during predictable and unpredictable conditions); and Stability limits (voluntary leaning tasks in standing with varying weight shifts in multiple directions using arm and trunk movement)[156].

The intervention period was divided into three blocks (A, B and C), in line with the progressive nature of the program. Block A (week 1-2) was an introduction period, where the participants were introduced to single-task balance exercises of each component of the program. In block B (week 3-6), dual-task exercises (combining concurrent cognitive and/or motor task whilst performing gait and balance exercise) were introduced to each component, further increasing difficulty. Finally, in block C (week 7-10), the amount of dual task was intensified and the difficulty level of exercises increased by combining different components (Table 5). All supervising physiotherapists were educated regarding the program and its inherent components, having the necessary practical application of theory.

Table 5. Overview of the blocks contained within the HiBalance program.

Block	Week	Standing	Walking	Dual Task
A	1	Stability limits	Motor agility	-
	2	APA	Sensory integration	-
B	3	Stability limits	Motor agility	C
	4	APA	Sensory integration	M
	5	Stability limits	Motor agility	C
	6	APA	Sensory integration	M
C	7	Stability limits		C + M
	8	Motor agility		
	9	APA		
	10	Sensory integration		

Dual task; performing several tasks simultaneously. C= Cognitive dual task (e.g adding counting to exercise). M = Motor dual task. Adding a motor task to exercise (e.g. carrying a tray or ball); APA= Anticipatory postural adjustments.

Each training session started with a five minute warm up containing basic cardiovascular exercises. The warm up was followed by highly-challenging exercises that consisted of walking and standing, the distribution depending on current component and block, for about 50 minutes (short brakes were included). To end the session, a five minute 'cool down' was performed, focusing on stretching, breathing and slow movements in sitting.

To conform to clinical practice, the participants in the intervention group received Physical Activity on Prescription (PAP) after the intervention ended. The PAP was attuned to each participant's interests, abilities and needs, and followed-up telephonically after 3 months.

4.6.1 Control group

The control group participants were instructed to maintain normal activity and daily living, and were not restricted in any way to participate in any other rehabilitation or training program.

4.7 DATA ANALYSIS

Statistical tests, analysis and compilation of descriptive data were performed using SPSS for Windows (SPSS Inc., Chicago, IL, USA) and R (R Core Team (2015), R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org/). Table 6 lists all descriptive statistics and statistical methods used in this thesis.

Table 6. Statistical methods used in the respective studies contained in this thesis.

	Paper I	**Paper II**	**Paper III**
Descriptive statistics			
Mean	•	•	•
Standard deviation	•	•	•
Median	•	•	
Frequency	•	•	•
25^{th}-75^{th} percentile	•	•	
95% Confidence interval	•	•	
Min-max		•	
Statistical methods			
Receiver operating characteristic curves	•		
Leave-one-out cross-validation	•		
Cohen's Kappa	•		
Independent samples T-test		•	•
Mann-Whitney U test		•	•
Spearman's rank correlation test		•	
Pearson Chi-Square			•
Multiple linear regression		•	•
Mixed ANOVA			•
Multilevel model			•

4.7.1 Paper I

Data regarding age, BMI, disease duration, disease severity and amount of medication were compiled for descriptive purposes. Since walking speed varied in every walking bout (on a group level) regardless of instructed speed, data restructuring were deemed necessary. Data was restructured using the 75th percentile of slow walking (1.04 m/s) as the lower threshold for normal speed, and the 25th percentile of brisk walking (1.31 m/s) as the higher threshold for normal speed. Thereafter Receiver Operating Characteristic (ROC) curves were used on restructured data to visualize a curve of the trade-off between sensitivity and specificity in each domain, and to determine the most sensitive and specific cut-off for the three walking speeds. Here, we used an approach that aims to maximize the specificity of the high accelerometer count cut-off (brisk), whereas for the low cut-off (low walking speed) sensitivity is maximized. This is a common procedure in calibration studies[121, 157-159], and was done on the basis that a false positive was considered worse than a false negative when it comes to a health-enhancing behaviour (brisk walking), whereas the opposite would apply for the low walking speed. Area under the curve (AUC), combined with confidence intervals was also calculated and reported. After cut-offs with the most beneficial sensitivity and specificity were defined, they were validated using a leave-one-out cross-validation. Calculated cut-offs on n-1 participants were tested on the individual left out where the predicted walking speed was compared to observed speed, thereby investigating the agreement. This was performed for all participants, followed by the calculation of a quadratic weighted Cohen's Kappa[160].

As supplementary analyses for this thesis, descriptive comparisons of both self-defined and post-restructured walking speed, as well as absolute agreement and quadratic weighted Kappa divided by sex, were derived.

4.7.2 Paper II

Descriptive data regarding demographic, disease-related and mobility-related factors were calculated, and variables from each domain were carried forward to either independent samples T-test or Mann-Whitney U-test to investigate differences between the classes if dichotomous, or utilized in a Spearman rank correlation test (if continuous) to ascertain associations to the two dependent variables, total PA (TAC) and brisk walking (minutes of walking >1.0 m/s). Dichotomous variables of near statistical significant differences between the categories regarding total PA or brisk walking, as well as those correlations with a p-value of <0.25, were inserted in two backwards entry linear regression models (one for each dependent variable). Age was controlled for in both models. Residual analysis showed heteroscedasticity and outliers, hence both dependent variables were square root transformed. No multicollinearity or leverage points were present.

Supplementary analysis comprised investigation of association between season and levels of PA at baseline, using both parametric and non-parametric testing (only results from t-tests reported).

4.7.3 Paper III

Data regarding demographics, disease related factors and factors related to physical function were summarized descriptively. A Mixed analysis of variance (ANOVA) was used to investigate short term effects of the intervention on total PA, brisk walking and sedentary behavior. Inspection of outliers was performed visually using boxplots and by calculating studentized residuals. Due to the presence of outliers within total PA and brisk walking, these variables were square root transformed before entered into the ANOVAs. To examine factors associated with a training effect on PA, T-tests were performed to analyse the difference between those increasing versus not increasing PA on the variables previously shown to be influenced by the intervention (balance control, step length and speed as well as UPDRS-ADL)[90] and season post-training. Further analysis was performed using a multiple linear regression, where associated factors to a difference in PA, was examined. The regression model was controlled for age, increased balance and the interaction term of group*season to investigate whether season alone had an effect on PA or was dependent on group affiliation.

The long term effects of the intervention on PA were analysed using a Multilevel model (maximum likelihood) approach. The model consisted of four fixed factors (time, group, time*group, season) and two random factors (intercept and time) to allow for both a random intercept and slope. The repeated covariance type was set to a first-order autoregressive (heterogeneous) structure, taking into account the higher correlation between measures closer in time compared to those further apart, and that variance was assumed heterogeneous. Comparison of model fit between nested models was performed using chi square goodness of fit test in order to find the most appropriate model (chi square results not reported).

Supplementary analysis comprised of calculating estimates of effect on brisk walking at each time point and the corresponding effect sizes using Cohen´s D as well as Hedges G.

5 RESULTS

In this section, results from the performed studies will be summarized, and some supplementary analyses will be presented. For a more detailed description of the results of each paper, please see the publications and manuscripts.

5.1 CALIBRATION OF THE GT3X+ ON OLDER ADULTS WITH PD

The data restructure procedure generated three speed intervals with a total of 88 performed bouts across 30 participants. Table 7 illustrates descriptive data of the self-selected and post-restructured speed intervals.

Table 7. Descriptive data of walking bouts before and after restructuring.

	Y-axis counts /15 sec[a]	VM counts / 15 sec[b]	Walking speed (km/h)	Heart rate (BPM)	Perceived exertion (RPE)
Self-defined					
Slow	332 ± 210	484 ± 242	3.3 ± 0.6	92 ± 18	12 (9-13)
Normal	548 ± 237	657 ± 251	4.2 ± 0.6	96 ± 19	13 (11-13)
Brisk	738 ± 273	847 ± 275	5.1 ± 0.8	104 ± 20	14 (13-15)
Post-restructuring					
≤1.04 m/s	256 ± 150	427 ± 230	3.2 ± 0.4	89 ± 17	13 (9–13)
1.05–1.30 m/s	574 ± 144	679 ± 176	4.2 ± 0.3	95 ± 18	13 (11–13)
≥1.31 m/s	819 ± 217	911 ± 232	5.3 ± 0.5	106 ± 19	13 (13–15)

All values are mean ± SD, except Perceived exertion which is defined as median (25^{th}-75^{th} percentile).[a]Y-axis counts per 15 seconds.[b]Vector magnitude counts per 15 seconds.

The performed ROC curve analysis generated two cut-points per axis, with a sensitivity of 100-68% and 89-64% and a specificity of 75-82% and 66-82%, attained for the Y-axis and VM, respectively (Figure 6). The leave-one out cross-validation showed an absolute agreement of 74% for Y-axis cut-points. Calculated cut-points are presented in Table 8 while the results from the quadratic weighted Kappa-analysis are displayed in Table 9.

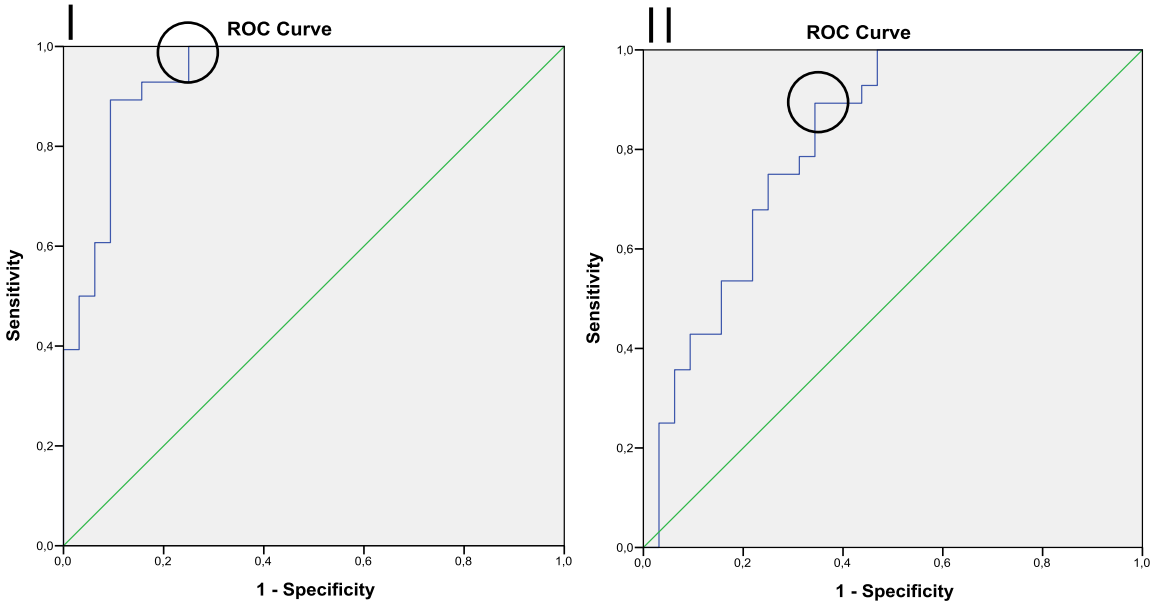

Figure 6. Examples of ROC curves from cut points for ≤1.04 m/s. I = Y-axis, II = VM.

Table 8. Derived cut points for each walking speed and axis.

Axis	Speed[a]	Sensitivity[b]	Specificity[b]	AUC (95%CI)[c]	Cut-point
Y[d]	≤ 1.04	100	75	0.940 (0.882-0.998)	≤ 328
	1.05-1.30				
	≥ 1.31	68	82	0.826 (0.716-0.936)	≥ 730
VM[e]	≤ 1.04	89	66	0.816 (0.708-0.923)	≤ 470
	1.05-1.30				
	≥ 1.31	64	82	0.784 (0.663-0.905)	≥ 851

[a]Meters / second (m/s). [b]Percent. [c]Area under the curve with 95% confidence interval. [d]Y-axis. [e]Vector magnitude.

Table 9. Agreement between cut-point calculated speed and actual walking speed.

Descriptives	Y-axis	Vector magnitude
Kappa[a]	0.792	0.691
SE[b]	0.049	0.068
95% CI low[c]	0.697	0.559
95% CI high[d]	0.888	0.824

[a]Quadratic weighted Cohen's Kappa coefficient. [b]Standard error. [c]Lower boundary of 95% confidence interval for the Kappa coefficient. [d]Higher boundary of 95% confidence interval for the Kappa coefficient.

Agreement separated by sex resulted in minor differences, with the largest found between the absolute agreement of the vector magnitude cut points. Kappa and absolute agreement are displayed in Table 10 below.

Table 10. Agreement of derived cut points stratified by sex.

Descriptives	Women		Men	
	Y-axis	**Vector magnitude**	**Y-axis**	**Vector magnitude**
Absolute agreement, %	74	62	73	67
Kappa[a]	0.790	0.667	0.787	0.710
Kappa SE[b]	0.079	0.108	0.066	0.091
Kappa 95% CI low[c]	0.635	0.456	0.658	0.531
Kappa 95% CI high[d]	0.944	0.878	0.915	0.889

[a]Quadratic weighted Cohen's Kappa coefficient. [b]Standard error. [c]Lower boundary of 95% confidence interval for the Kappa coefficient. [d]Higher boundary of 95% confidence interval for the Kappa coefficient.

5.2 FACTORS ASSOCIATED TO PHYSICAL ACTIVITY AT BASELINE AND EFFECTS OF INTERVENTION

Wear time, total PA and percentage of time in sedentary, illustrated by total numbers as well as separated by group for all time points, are presented in Table 11. Sedentary bouts (≥10 minutes of sedentary) and bouts of brisk walking (≥10 minutes of activity corresponding to brisk walking) spanned from 12-15 bouts per day and 0.51-0.98 bouts per day, respectively, over the course of the study. The number of brisk walking minutes for each measurement time is presented in Figure 7.

Table 11. Wear time, sedentary and total PA of all participants with valid data, for the entire sample and when separated by group, at all time-points.

Groups	Wear time[a]	Sedentary[b]	Total PA[c]
at Baseline			
Total sample (n=83)	828 (80)	75 (8)	286445 (143839)
-Intervention (n=43)	851 (91)	75 (7)	322094 (114383)
-Control (n=40)	806 (64)	74 (10)	299528 (159962)
at Post-intervention			
Total sample (n=74)	825 (87)	73 (8)	303685 (162261)
-Intervention (n=39)	841 (86)	72 (9)	363102 (175930)
-Control (n=35)	811 (87)	75 (7)	280490 (139463)
at 6 month follow-up			
Total sample (n=67)	832 (75)	76 (8)	279150 (129247)
-Intervention (n=36)	842 (74)	74 (7)	314822 (124716)
-Control (n=31)	823 (77)	77 (8)	262485 (138947)
at 12 month follow-up			
Total sample (n=66)	824 (92)	76 (8)	262338 (137232)
-Intervention (n=34)	844 (84)	75 (8)	320444 (138637)
-Control (n=32)	804 (97)	76 (9)	252497 (135432)

All values presented as mean (SD). [a]In minutes per day. [b]In percentage of wear time. [c]In vector magnitude counts per day.

Figure 7. Mean minutes of brisk walking and 95% confidence interval (error bars) for the intervention and control group at all measurement points.

The primary analysis using t-tests to investigate mean differences, in **Paper II**, showed that those with dyskinesia and with a partner had higher total PA compared to those without (p=0.02 and 0.19, respectively), and those with a H&Y-score of 2, compared to 3, had a higher number of brisk walking minutes, although insignificant (p=0.22). The correlation analysis showed nine and eight variables correlating to total PA and brisk walking, respectively. The following analysis using multiple linear regression resulted in adjusted R^2 values of 0.34 and 0.22, and gave way to four (and one near significant - balance control, p=0.06) and two significant associated factors, of total PA and brisk walking respectively (Table 12).

Table 12. Correlates of total PA and brisk walking using multiple linear regression.

Correlates	***B***	***Beta***	***p***	**95% CI for *B***	
				Lower	**Upper**
TOTAL PA					
Constant	709.94	-	<0.01	224.10	1195.78
Motor impairment[1]	-3.54	-0.28	<0.01	-5.85	-1.23
Physical function[2]	1.68	0.24	0.01	0.36	3.00
BMI[3]	-7.34	-0.24	0.01	-13.00	-1.68
Dyskinesia[4]	73.04	0.22	0.03	6.00	140.10
Balance control[5]	7.75	0.19	0.06	-0.31	15.82
BRISK WALKING					
Constant	1.96	-	0.61	-5.70	9.61
Physical function[2]	0.04	0.32	<0.01	0.02	0.07
Balance control[5]	0.19	0.26	0.02	0.04	0.35

[1]UPDRS motor score. [2]SF-36 Physical function score. [3]Body Mass Index. [4]Dichotomized (0=no dyskinesia, or 1=dyskinesia). [5]Mini-BESTest total score.

A difference in absolute numbers between total PA and brisk walking at different seasons of the year during baseline was seen, though the distribution was wide and there were no significant differences between the seasons regardless of outcome (Figure 8.)

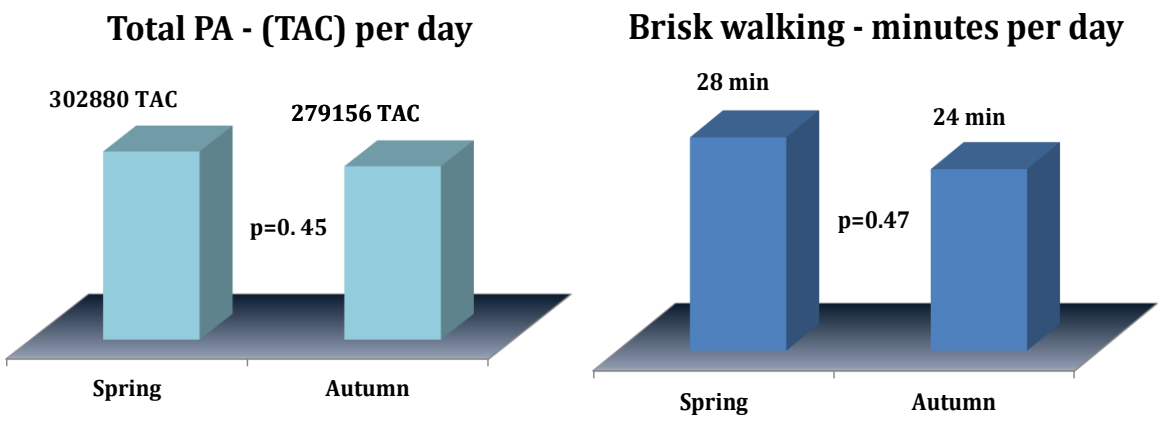

Figure 8. Amount of PA at baseline separated by season for total PA and brisk walking.

The ANOVA, investigating short-term effects of the HiBalance program, showed a significant interaction effect between group and time for brisk walking ($p<0.01$), indicating a higher amount of brisk walking in the intervention group. All other outcome variables had insignificant interaction effects (total PA $p=0.21$; brisk walking bouts per day $p=0.35$; sedentary per day $p=0.19$; sedentary bouts per day $p=0.53$). The examination of factors associated with a training effect on PA, using a multiple linear regression showed that the emergent difference in brisk walking between baseline and post-intervention was associated to group affiliation and season ($p<0.01$ for both variables), with the association of each one of these variables being independent of the other (interaction term season*group $p=0.25$).

The long-term effect analysis (Multilevel model) resulted in a significant overall interaction term (group*time) for brisk walking ($p=0.04$), indicating that the intervention group increased their amount of brisk walking, in comparison to the control. All other outcomes had insignificant interactions (total PA, $p=0.43$; sedentary time, $p=0.27$; time in sedentary bouts, $p=0.36$; bouts of brisk walking, $p=0.21$). Table 13 displays interaction effects between each time point for brisk walking, along with respective effect sizes.

Table 13. Estimates and effect sizes for brisk walking at all time points.

Parameter	Estimate	P-value	CI 95%	1st effect size[1]	2nd effect size[2]
I-group*PI[a]	10.04	0.04	0.59 - 19.48	0.34	0.34
I-group*6m[b]	8.23	0.02	1.38 - 15.08	0.36	0.35
I-group*12m[c]	3.63	0.43	-5.52 - 12.78	0.15	0.15

[1]Effect size calculated using Cohen's D on mean values and SD for each group and time point. [2]Effect size calculated using Hedges G. Control group and baseline measures were set as reference categories. [a]Intervention group*post-intervention. [b]Intervention group*6 month measure. [c]Intervention group*12 month measure.

6 DISCUSSION

The discussion presented here will cover a few subjects similar to the discussions of the papers, yet is more of a speculative nature and will to a greater degree focus on absent results, some specific parts of the results in comparison to other studies as well as factors of interest that were not explored in this thesis. For further discussion of main findings and methods, please see **Paper I-III**.

6.1 OVERALL FINDINGS

The results derived from the calibration part of the thesis suggested sensitive, specific and cross-validated cut points for both the vertical axis and vector magnitude of the Actigraph GT3X+, to be utilized when measuring habitual PA in older adults with PD. According to the results, the Y-axis cut points showed greater sensitivity and specificity than that of the VM.

The investigation of correlates of PA demonstrated that factors associated with total PA and brisk walking differs, and that some of these are potentially modifiable, while a consequence of medication, such as dyskinesia, may dilute the signal and perhaps also lead to false conclusions. Adding on, the evaluation of short-and long-term effects of the HiBalance program revealed that PA increased in the intervention, in comparison to the control group, yet of all factors investigated, only brisk walking was influenced, with the effect not lasting after six months. Further, analysis of factors related to a training effect on brisk walking demonstrated that group affiliation and season at the end of the intervention was independently associated to an increased PA, while there was no relation to an improvement in balance control.

6.2 GENERATED CUT POINTS FOR PA MEASUREMENT

Although accelerometry is not suitable for all types of human movement, such as weight lifting or cycling[161], the methodology is still suitable for classifying activity intensity of older adults, and is even considered a gold standard by some[162]. However, problems incorporated in the method arise when aiming to extrapolate and infer some form of physiological or functional meaning from gathered data. There are distinct opinions regarding best practice when validating or calibrating an accelerometer. On one hand, researchers suggest that if time in different intensities of activity is the primary interest, then calorimetry should be used as criterion measure[163]. On the other side of the spectrum are those who support a view of movement sensors as an instrument measuring a biomechanical aspect of PA, and therefore propagate against using a physiological measure as the primary comparison[44]. Also, instead of using the more conservative cut point-generating method, it has been argued that pattern

recognition is the way forward in the future and should be the first-hand choice, even though this methodology is questioned by other researchers due to the limited validity in free-living settings[45].

Based on the author's observation of a previously used method where older adults were instructed to walk on treadmills whilst being measured using indirect calorimetry (oxygen consumption), to assess energy expenditure at different walking speeds, it was decided not to use this type of methodology in **Paper I**. A great number of the observed older adults had never used a treadmill before, hence it altered their walking pattern to a great extent, thus presumably influencing their physical effort. This was believed a danger to the inherent validity, and would perhaps pose an even greater problem in older adults with PD, such they already suffer from gait dysfunction and/or balance impairment. Therefore the method of free in-door walking was chosen as criterion measure. Nonetheless, the chosen methodology can also be questioned. The great gait variability in older adults with PD may influence the effort of walking in different speeds, thereby inducing variation in intensity of performed activity. Consequently, intensity of each walking speed is harder to establish, and determining intensity is the more common approach of calibration studies.

In the light of these valid arguments against the current methodology, no assumptions of these cut-points being related to known PA intensities are made. Other data such as perceived exertion and heart rate during walking, were sampled in the study, unfortunately these were unreliable measures in our sample due to great variation. If reliable, they could have served as criterion measures for intensity. Instead, the generated cut points may serve as a proxy for quantifying and separating health-enhancing behaviours (brisk walking) from behaviours associated with poor health (low walking speed)[164, 165]. If physiological intensity of PA is the main interest in this population of older adults with a progressive disease, including increased debilitation of mobility over time, perhaps some sort of recurrent individual calibration should be performed. Such a methodology could increase accuracy, yet would also require more resources.

By utilizing ROC-curves, the optimal cut-points for each walking speed were defined. An approach that aims to maximize the specificity of the high threshold (brisk) was used, whereas for the low threshold (low walking speed) maximization of sensitivity was chosen. This was done on the basis that a false positive was considered worse than a false negative when it comes to a health-enhancing behavior (brisk walking), whereas the opposite would apply for low walking speed. This type of adjustment of sensitivity and specificity is common and has been applied in previous calibration studies[121, 157, 158], yet it is important to note that misclassification cannot be ruled out, since neither the sensitivity nor specificity was 100%. Adding on, the use of the leave-one-out cross validation combined with a quadratic weighted Kappa is a strength of this calibration study. The resultant sample size matches other accelerometer calibration studies fairly well[121-124], and the chosen type of validation also permits all participants to contribute to the data, contrary to other types of cross-validation that consume participants to test generated cut points.

In **Paper II** and **III** the vertical axis cut point >328 counts / 15 sec were used to define brisk walking (>1.0 m/s), which ordinarily was the top threshold for the lowest walking speed (<1.04 m/s). This was performed to further align the cut point and estimated walking speed to the threshold of 1.0 m/s, considering an individual's self-selected walking speed is indicative of functional status[166], with walking speed <1.0 m/s predicting cognitive decline in 5 years and risk of hospitalization in 1 year[167], while walking >1.0 m/s is associated with greater survival in older adults[164]. In point of fact, the threshold of 1.0 m/s has also been used in previous studies as a boundary between slow and brisk usual walking speed in older adults[168].

6.3 CORRELATES OF PA IN PD

6.3.1 Body Mass Index

Paper II adds to the body of knowledge concerning associated factors of PA. Some factors, such as motor impairment and physical function, had previously been reported as significant contributors to the variance of PA[95], while others constituted more novel findings. BMI and its relation to PA had not been investigated in older adults with PD before, although both weight and height may be negatively affected by increased disease severity due to weight loss and stooped posture[169, 170], coupling with a decrease in PA. Further, in the overall population, overweight / obesity is associated with lower levels of PA and inactivity[26], and BMI has previously shown to be inversely associated to level of PA in adults, an association that strengthens with time[171]. In **Paper II**, results showed a significant relationship between BMI and total PA, interpreted as a decrease in total PA with increased BMI. However, the relation to brisk walking was insignificant. In the measure of total PA, all types of habitual activity are included, even sedentary, at least in a theoretical sense. As an analysis of other types of PA or sedentary was not included in the scope of **Paper II**, it is unknown whether some of the other sub-measures also relate to BMI. Furthermore, it is important to consider that the measure of weight and height in the BETA PD-study were performed with clothes and in-door shoes on, hence the measure may be somewhat inaccurate.

6.3.2 Disease duration

Due to the debilitating consequences of PD, specifically those relating to activity limitations and the fact that the disease progresses over time, a relationship between disease duration and PA would seem intuitive. However, this was not confirmed in **Paper II**, since there was no significant correlation between disease duration and total PA, nor brisk walking. This result is in line with previous research findings indicating the lack of a correlation between objectively measured energy expenditure and time since diagnosis[106]. Potential reasons for the lack of relationship may be the chosen method of disease duration measurement in the current thesis, and the difficulty associated with procedures for diagnosing PD. In the RCT of the BETA-PD study, date of diagnosis by neurologist was mainly based on self-report. Naturally, many

factors may influence the time or date of diagnosis, such as when symptoms were first acknowledged, how long the patient waited to see a neurologist, etcetera. Also, accurate self-report of diagnosis is dependent upon memory function, and since most older adults with PD will eventually develop cognitive impairment affecting not only executive function but also memory[172], the level of accuracy could be questioned. Even though some participants contributed with medical journals reporting date of diagnosis, there may still be a variation of disease severity within disease duration, hence complicating the analysis of its association to PA.

6.3.3 Depression and its measure

As with other sub-studies of RCT's, the available correlates to be analyzed were somewhat limited. This naturally hindered inclusion of other factors of interest. A factor evidently correlated to the level of PA in adults is depression. Reportedly, depression is linked to increased sedentary behavior and inactivity, while it is more common later in life and also more prevalent in those with a chronic disease[173, 174]. Depression in PD is thought of as having more of a biological basis, rather than an emotional reactive one, and could partly be the consequence of loss of dopamine and noradrenaline innervation in limbic structures of the brain[175, 176]. As such, depression is a common non-motor symptom of PD, reportedly found in about 40% of older adults with PD, in comparison to only 10% in geriatric patients without PD[177]. Even though the prevalence can vary between 3-90% in PD, depending on the study, the average prevalence is still considered substantial, and is believed to be underdiagnosed[178].

In the current thesis, depression was assessed using the Swedish GDS. Although there are many alternatives, the GDS is a scale frequently used within studies of depression in PD[150]. Yet, it may be insensitive to severe depression and utilizing it in people with PD may be complicated due to overlapping of symptoms with the disease itself. Also, its content validity can be questioned since there is limited concordance between GDS items and Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV)[179]. Perhaps these potential weaknesses are part of the reason for the non-significant correlation to PA (results reported in **Paper II**), and a more encompassing measure of depression is needed to establish an association. Or perhaps the results suggest that since accelerometry captures a dimension of movement, the types of measurements related to motor skills and ambulatory activity are more closely related to objectively assessed PA than self-assessed measurements (questionnaires or interviews). In point of fact, a study from 2011 showing a significant relation between PA and the GDS score in PD based the results on a subjective measure of PA[100], whilst another performed in 2013, also in PD but utilizing an activity monitor, reported insignificant findings[109]. Whatever the reason for the lack of a significant finding between these two measures when the opposite is expected, this non-motor symptom is of great clinical importance, since it is not only detrimental to overall health and health-enhancing behavior such as PA, but also pharmacologically treatable.

6.3.4 Sleep and accelerometry

Another relevant factor of interest in PD is sleep. According to the second stage of the pathological process of PD, as interpreted by Braak et al (2003), the pathology advance from the olfactory bulb to the lower brainstem, thereby inflicting symptoms of autonomic characteristics, as well as sleep disturbance[180]. A majority of persons with PD suffer from disturbed sleep, with estimations varying between 74-81%, and disturbances are often seen at an early onset of disease[181]. The most common form of insomnia in PD is sleep fragmentation, where frequent awakenings during the night are common. It is believed that the cause of sleep fragmentation is multifactorial, and could be because of, but not limited to, the inability to turn at night, bradykinesia and rigidity, and effects of medication. Therefore, treatment is based on targeting the probable cause of the sleep disturbance[182].

The availability of accelerometers that are able to quantify sleep has steadily increased the last decade. The measure of sleep, when using accelerometers, is based on lack of body movement at night[183]. If aiming to measure sleep using an accelerometer, it is recommended that a wrist-worn accelerometer is used and that data are collected for several days, during all 24 hours[184]. The measure of sleep using wrist-worn accelerometers has been validated against polysomnography, or other established methods of sleep assessment such as sleep diaries or videosomnography. The collection of evidence support that accelerometry is useful in the estimation of sleep percentage, total sleep time and wake after sleep onset (WASO)[184].

This trail of thought leads to the idea that sleep disturbance, for instance WASO or sleep fragmentation, is possible to quantify in older adults with PD. Due to the risk of increased participant burden, no sleep diary or other measure of sleep was included in the RCT. Adding on, because of the potential interference upper extremity tremors, waist worn accelerometers were chosen. Considering that exercise or PA has shown to be beneficial for sleep, in both adults and older adults[185-187], and that evidence also exist for the inverse relationship[188], this association would be interesting to investigate in older adults with PD. In future studies of the same population, accelerometric measures of PA, coupled with a sleep diary and instructions indicating the wearing of accelerometers 24 hours per day, would enable analysis of associations to PA and establish the effect of an intervention and/or associations to other potential variables of interest.

6.4 EFFECTS OF BALANCE TRAINING ON PHYSICAL ACTIVITY

6.4.1 Effects on brisk walking

The results from the short- and long-term evaluation regarding PA correspond with the previous short-term evaluation of the HiBalance program, in the sense that the progressive balance training led to an increase in ambulatory activity, while the control group decreased their amount of ambulation[90]. Interestingly, in **Paper III** no significant effect on sedentary behavior was observed. The wake hours of the day contain a certain amount of PA of

different types and intensities mixed with sedentary, which is more or less fixed, unless sleep duration is altered. If the amount of brisk walking is altered due to participation in an intervention, naturally some other behavior or activity type must decrease[189]. The results herein, reporting non-significant findings for total PA and sedentary, leads to further questions surrounding chosen methods. In the current methodology, some other PA variable was altered in amount by the intervention but it was missed or left unmeasured, or there were small changes in each sub-level of PA and sedentary that separately did not reach significance. This could be of great interest since it is not only the type of activity that is increased that matters to the overall effect on health, but also what it substitutes. Although being out of scope for this thesis, some form of analysis of substitutional effects on accelerometer data after intervention would be highly interesting in order to more profoundly understand the results.

Adding on, since PA of a certain intensity and level is thought of as a protectant behavior from the undesirable effects of sedentary on health[24], even if sedentary was not decreased by the intervention, the results are hopeful. Yet, it is unknown whether the amount of increase in brisk walking is of clinical importance, since at the moment there are no guidelines or recommended levels of PA that signifies a minimal clinical difference for older adults with PD. For adults in general, pooled results of more than half a million individuals suggest that amounts of PA lower than the official recommendation still leads to a decreased risk of mortality by 20%[13], raising hope for RCTs reporting significant yet small effects on PA.

The results reporting a significant association between season and difference in PA are clinically valuable, yet become harder to interpret, when considering that there was no significant difference at baseline between those measured during winter season compared to summer. This difference could be due to differing outcomes (absolute activity at one specific moment compared to a difference between two time points) and/or that the sample of each paper are not the same.

6.4.2 Balance training and physical activity

The potential effect of balance training on PA was anticipated due to previously reported benefits, though it was hypothesized – as suggested by previous research – that an increase of PA would be due to an increase in balance performance, by allowing the ability to be active in daily living[92]. Yet the results from the analysis of training effects show otherwise, i.e. no association. Previous investigations of training effects in analogous populations have reported beneficial effects on objectively measured level of PA, amount of walking and subjectively measured ADL. Two contained follow-up measures of different quantities, and one reported a dissipation of effect with time, as in **Paper III**[111, 190, 191]. Adding on, the two papers containing effect size measures reported a Cohen's D of 0.35 for walking >10 seconds / minute after home cueing training, and a Hedges G of 0.40 on self-assessed ADL after an intervention described as physical therapy. These levels are in line with what were reported in

this thesis. Furthermore, considering that PA was a secondary outcome in our RCT and not the main aim of the intervention, the effects on brisk walking are of a respectable magnitude.

Although interventions between studies differ, the results discussed above suggest that a form of repeated, structured and challenging exercise leads to increased habitual PA or an increased self-perceived ability to perform ADL. In the current study, the actual mechanism of the fallout is unclear (apart from the effect of season which is independent on the intervention), yet a probable contributing factor to the observed increase is a continuous and progressive challenge to the cardiorespiratory and musculoskeletal system that the HiBalance program may entail for a great majority of the participants. The experience of being a trainer in the program led to the assumption that many participants were not accustomed to this level of exercise several times a week, yet increased fitness over time may have helped in the management of exercise as the program progressed. In point of fact, we evaluated training progression using accelerometers on a smaller sample of participants (n=10) showing significant progression of activity during the HiBalance program (results not yet published). This is further confirmed by interviews performed with the participants, where findings suggests that participants acknowledged the importance of PA to counter the disease and described the program as pushing them to the edge of their capability[192].

Concludingly, if feasible, future studies would benefit from continuous measurement of heart rate or other measure of exertion during intervention and/or some type of exercise progression measurement, as well as cardiorespiratory testing pre- and post-intervention.

6.5 METHODOLOGICAL CONSIDERATIONS

6.5.1 Internal validity

The level of dopaminergic medication in older adults with PD differs between individuals, and the responsiveness of medication may vary over the day, e.g. due to differences in disease severity, time of onset or sex[193, 194]. Hence, the reduction of motor symptoms due to medication is not constant. In the study described in **Paper I**, participants' level of medication was descriptively outlined yet not controlled for in any way. Although individuals were verbally instructed to medicate as usual, so as to capture their normal state, there may have been a variation of walking ability due to testing that took place at different times of the day. Albeit this may have affected the generated data and therefore also the cut points, the potential effect of this on accelerometer sampling of all walking during a week is difficult to fathom. Perhaps it would have been an even greater error to adjust level of medication beforehand, since the resultant cut points are intended for all-day measurement over a seven day period.

The approach of utilizing in-door walking in **Paper I** may be debatable. When designing the study, considerations of using out-door walking was discussed. Still, in-door walking was chosen for several reasons. Firstly, a pragmatic approach was that weather would not affect the measurement, and considering the study was performed during the autumn/winter of 2013, the climate could have affected results as well as being a potential hazard for some participants, due to increased risk of falling. Secondly, walking out-doors would probably include changes in altitude, which would reflect free-living walking out-doors. Yet, this would perhaps also have an effect on the participants' exertion and walking speed, which in turn could change their ability to walk at higher speed. Instead, in-door walking was the method of choice, since more of the environmental factors could be controlled, such as the traffic of people, sudden obstacles, etcetera, thereby allowing a more constant walking speed and a steady flow of walking, which helped with the calculation of overall walking speed during each bout.

The level of explained variance of the two regression models in **Paper II** proposes that there are other factors to be considered which were not included or measured in this study. There are a limited number of other studies exploring associated factors of PA in PD and where a linear regression has been utilized as means of main analysis. Those found in the literature report a variance ranging 24-69% of total PA or energy expenditure in PD[95, 106], and about 30% of explained variance of PA in persons with ischemic stroke[195]. Although this study does not encompass the full spectrum of associated factors for PA in PD, the levels of variance reported are in line with previous studies, as well as adding to the body of knowledge.

Although accelerometry is considered by many a preferred tool of PA measurement, is easy to use and has high sensitivity for detecting changes in PA (irrespective of cut point choice)[196], some aspects of the methodology are not as well established as other popular methods such as direct observation or the use of surveys[197]. As such, a potential obstacle for valid measurement is the definition of wear time, where, in the current thesis, it is defined using the recommended suggestions from Choi et al (2011)[129]. In general, the cleaning process of accelerometer data may lead to the exclusion of participants by classifying them as non-wearers, despite wearing the accelerometer. This may lead to bias and less data for analysis. One way to combat this is using visual evaluation of wear diaries and data, as in the current thesis, which has proven to be a highly valid method of choice[198]. These safety measures regarding data may help in securing some internal validity, yet other biases related to PA measurement is harder to control for, such as social desirability, signifying that participants knew of being monitored, hence increasing activity during the measurement period in order to seem more active.

Using a waist-worn accelerometer leads to problems measuring certain types of activities, such as carrying a load, bicycling or swimming. This entails a less exact measure of activity during the day, if these activities are commonly performed by the wearer. Yet, the choice of walking as the outcome or criterion measure was due to it being the most common PA

performed in older adults[199], and therefore should be the primary behavior of focus. Optimally, all behaviors should be measured as exact as possible using one instrument and wearing position, yet until this is possible for the overall end-user, the researcher must make a choice of what is most interesting to capture. Also, considering that intensity of each walking speed is unknown due to the method of choice, and may vary by cause of the heterogeneity of the symptoms in the population under study[200], calculating the number of participants reaching recommended levels of MVPA is problematic.

A threat to internal validity related to the RCT of the BETA-PD and therefore also to **Paper III** was that the test assessors were not blinded to group allocation of participants during follow-up measurements, considering that some testers also served as trainers in the intervention. Although testers never assessed a person involved in their training group, it may still have biased the results of some measures performed during laboratory testing, such as balance performance. This shortcoming was avoided with regards to PA measurements, due to the use of an objective instrument. Yet, due to the study methodology, participants themselves were not blinded with regards to group allocation, which is a common problem in exercise interventions.

6.5.2 External validity

A representative sample is necessary to draw conclusions for the population at large. As previously reported, older adults with mild-to-moderate disease severity were included in the current studies. The inclusion was also based upon a clinical evaluation of balance performance. Further, since participants were recruited using advertising, it is probable that those joining the study are primarily persons interested in interventions or research, or those not suffering from depressive symptoms influencing their motivation. Adding on, all individuals with signs of cognitive deficits were excluded, as well as those using some form of walking aid, which further limits generalisation of the sample. Therefore the sample may be considered more of a sub-group of older adults with PD, rather than representing the overall population. In point of fact, according to previous evidence, participants in clinical trials are often healthier and are of higher educational background in comparison to the general population[201]. Considering all these arguments, demographic data of the samples included herein seem to match other studies performed in Sweden and Europe quite well[202, 203].

Although drop outs may be problematic due to its potential effect on the power of the study, according to previously performed drop-out analysis of the RCT of the BETA-PD short-term, data were missing at random (results not presented here). The amount of missing accelerometer data over the course of the RCT was more or less stable over the time-points, varying between 5-8 and 4-9 missing measurements per time point in the intervention and control group, respectively. Still, some types of analyse, such as the ANOVA, exclude participants if data are missing for one measurement point. One way to handle this is to

impute data using e.g. multiple imputation, or a statistical model that is able to handle missing data, such as a multilevel model (as in **Paper III**). This type of analysis allows all participants measured to remain included without the need for imputation, thereby contributing to the variance as much as possible. Yet, the existence of drop outs is still a problem to the external validity of any study, since it may dilute the initial randomization and thereby influence the ability to generalise the results to the population at large.

In Sweden, there is a distinct seasonal difference in climate. Winters are cold, resulting in larger number of falls in older adults due to slipping on ice or snow [204]. The evidence of an association of seasonal nature on the training effect on PA may be linked to the older adults' fear of ambulating outdoors during winter, supported by the fact that active elderly in Sweden attain injuries outdoors more often during winter[205]. This potential effect of the environment on PA may not apply to older adults with PD in other countries or continents with a different climate.

Another probable contextual threat to external validity is that the intervention of the RCT was performed in a clinical context (a university hospital), which entailed access to clinically experienced trainers and equipment needed to perform such an intervention in an optimal manner. Yet the amount of resources available was most likely larger compared to regular clinical practice. Due to the RCT being an efficacy trial, it tests whether the intervention can have an effect in an ideal surrounding, implicating the problem with generalisation of the results to other conditions or environments. To measure the degree of beneficial effect in other contexts, an effectiveness trial (or pragmatic trial) is required[206].

6.6 IMPLICATIONS FOR CLINICAL PRACTICE

- The generated cut points allow measurement of habitual walking in different walking speeds of patients with PD, in order to assess PA as well as mapping out the individuals' activity patterns. Advisably, the vertical axis cut points should be used, due to higher accuracy in comparison to that of the VM. The cut points are easily accessible for all users of Actigraph accelerometers in the appurtenant software ActiLife.

- The results suggest that physical function is closely related to PA, due to its significant association to both total PA and brisk walking. Although the causational direction of the association is unknown, the relation between these two modifiable factors is promising for clinical practice.

- The reported association of dyskinesia with higher levels of total PA proposes that clinicians should be aware of the potential repercussion of this symptom on measured PA, and if possible, control for its effect.

- When planning balance training, season at the time of intervention should be considered, since completion of training during spring or summer may have a beneficial effect on amount of ambulation in free-living.

- The effect of the HiBalance program on the amount of brisk walking dissipates after six months. Hence, recurrent exercising is recommended if one is to avoid participants returning to their levels before training.

6.7 FUTURE RESEARCH

- The use of accelerometers in PA measurement is increasing in popularity[197], and the methodology is steadily evolving and being improved. Concurrently, more sophisticated and reliable ways of data analysis are being developed, yet these new methods seldom reach the end-user. Future studies in this area would benefit from closing the gap between methods such as pattern recognition and the clinician needing easy access to exact data on patients' PA. Furthermore, subjective measures of motor impairment has flaws and could be improved if coupled with a wearable sensor, which add advantages such as continous and objective surveillance of symptoms[207], whilst simultaneously gathering PA data.

- It would be of value if future studies further investigate associated factors to objectively measured PA in older adults with PD, proposedly with a focus on socio-cultural, environmental and behavioral factors that may influence activity. The sample's representativeness should be a top priority. Such an investigation would help further in understanding the behavior of PA in this population and lead to findings of potential mediators and modifiable factors.

- The short and long term effects on PA are of clinical interest, and although effect sizes are moderate, it is unknown whether the increase reaches a minimal clinical change, since, to date, no such standard has been postulated. Defining such a cut-off would be highly useful for future evaluation of interventions.

- Although an increase in habitual PA is promising, proposedly the next step is to investigate and develop interventions and strategies aimed at maintaining this change. Recurrent training, or exercise referral as well as exploring which behavioral factors need to be targeted, could be potential approaches to establish sustainable changes in PA.

7 CONCLUSIONS

This thesis suggests sensitive and specific cut points (available in the appurtenant Actigraph software) for objective measurement of habitual PA in older adults with PD to be used in either epidemiological studies or as a main outcome measure in clinical trials. Further, results of the thesis add to the body of knowledge surrounding correlates of PA in the same population, confirming the association with disease severity, as well as suggesting that dyskinesia should be controlled for when measuring total PA with accelerometers, in order to draw valid conclusions.

The HiBalance program is a progressive and highly-challenging exercise intervention aimed at increasing balance control in older adults with PD. The program shows beneficial effects on amount of brisk walking that is maintained over a 6 month period that unfortunately dissipates thereafter. This suggests that balance training should be performed regularly to maintain the potential effect on health preserving PA. Adding on, the increase in ambulatory activity after the intervention is not associated with an improvement in balance performance. Instead it seems that the season of training – during spring – has a positive effect on ambulatory activity, independent of group affiliation.

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